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PIA NYNÄS

Clinical Findings in Subjects with Workplace Moisture Damage Related Symptoms

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F114
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 26th January 2024, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Tampere University Hospital, Departments of Occupational Medicine and Phoniatrics and Allergy Centre
Finland

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-3207-5 (print)
ISBN 978-952-03-3208-2 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-3208-2

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2023

To my family

KIITOKSET (ACKNOWLEDGEMENTS)

Tämä väitöskirjatutkimus on toteutettu Tampereen Yliopiston lääketieteen ja terveysteknologian tiedekunnan sekä Tampereen yliopistollisen sairaalan työlääketieteen poliklinikan, allergiakeskuksen ja foniatrian poliklinikan yhteistyönä. Tutkimusta ovat tukeneet Tampereen tuberkuloosisäätiö, Pirkanmaan sairaanhoitopiiri myöntämällä tukea valtion tutkimusrahoituksesta, Orionin tutkimussäätiö, Suomen lääketieteen säätiö, Keuhkosairauksien tutkimussäätiö ja Korvatautien tutkimussäätiö.

Kiitän sydämestäni tutkimuspotilaita, jotka ovat aikaansa ja vaivaansa säästämättä osallistuneet tutkimukseen. Kiitän myös väestöverrokkeja ja oireettomia verrokkeja merkittävästä panoksestaan tutkimuksen onnistumisessa.

Työkaverit Työterveyslaitoksella, erityisesti Marjaana Lahtinen, Aki Vuokko, Minna Pihlajamäki ja Eero Palomäki, kiitos kokemustenne jakamisesta ja käytännön avusta. Erityiskiitos Tattilan huipputiimille! Kiitos korvaamattomasta työstä tutkimuspotilaiden prosessissa Työterveyslaitoksen lähimmälle kollegalleni Kirsi Koskelalle, työlääketieteen poliklinikan vastaava hoitaja Marjo Mäkiselle ja sihteeri Sanna Jäväjälle. Tom Oikarinen, kiitos työkaveruudesta ja idearikkaista keskusteluista.

Tutkimushoitajat Tiina Mäki, Piitu Oksanen ja Merja Rumpunen, kiitos korvaamattomasta työstänne potilaiden tutkimusten organisoinnissa. Tutkimuskoordinaattori Tina Katto, kiitos arvokkaasta avustasi lupaprosessien ja rekistereiden syövereissä.

Tutkimusryhmä, jonka kantavina voimina on halu tehdä laadukasta tutkimusta, huippuosaaminen, auttaminen ja sopivassa määrin myös huumori, on loistava paikka kokemattomalle tutkijalle kehittyä eteenpäin. Professori Lauri Lehtimäki, olet itseäsi säästämättä ollut aina valmis auttamaan. Sinulla on upea kyky prosessoida monitahoiset asiat ja tehdä niistä selkeitä, eteenpäin vieviä johtopäätöksiä. Dosentti Jura Numminen, kiitos, että olet tuonut rauhallisen ja ansiokkaan osaamisesi tutkimusryhmäämme. LT, erikoislääkäri Antti Tikkakoski, kiitos väsymättömästä avustasi, kannustuksestasi ja it-osaamisesi jakamisesta. Dosentti Leenamaija Kleemolaa ja FT, puheterapeutti Elina Kankare, tietämykseni foniatriasta on moninkertaistunut rauhallisen ja selkeän tutkimusotteenne ansiosta, kiitos siitä.

Foniatrian erikoislääkäri Sarkku Vilpas, olen ollut vaikuttunut paneutumisestasi potilaiden tutkimiseen ja halustasi toimia heidän parhaakseen. Kiitos tuestasi ja väsymättömästä kannustuksestasi, jota olen vuosien aikana sinulta saanut.

Yliopisto-opettaja, biostatistikko Heini Huhtala ja dosentti Anna-Maija Haapala, kiitos tärkeästä panoksestanne artikkeleiden työstämisessä.

Olen syvästi kiitollinen ohjaajalleni professori emeritus Jukka Uitille, jonka myötävaikutuksella aloitin työskentelyn Työterveyslaitoksella. Jukka, laaja sivistyneisyytesi, ihmisten kohtaaminen ja valmius syventyä keskusteluihin ovat tehneet minuun pysyvän vaikutuksen puhumattakaan siitä, kuinka laajan tieteellisen ja käytännön kokemuksesi pohjalta olet aina antanut apua aikaasi säästämättä.

Väitöskirjani esitarkastaja dosentti Irmeli Lindström, kiitos huolellisesta paneutumisestasi työhösi kirjan tarkastajana. Sen ansiosta kirjastani tuli paljon selkeämpi ja informatiivisempi. Professori Kari Reijula, kiitos esitarkastajana antamistasi rohkaisevista, positiivisista sanoistasi.

Kiitos ystävät, erityisesti Tiina Koivisto kaiken maailman keskusteluista ja tutkimustyön oivallusten jakamisesta; Johanna Tuukkanen ja Hannu Penttilä hienoista reissuista pyörän päällä ja ilman, juustoja ja viinejä unohtamatta; Tuija ja Antti Brax vapuista, juhannuksista, juhlista, arjesta, tuestanne. Te perheinenne olette tärkeä osa elämääni.

Kiitos kaikki Karjalaiset, Selkeet ja Nynäsit tuesta ja kannustuksesta. Äiti, kiitos, että olet esimerkilläsi opettanut avarakatseisuutta, rohkeutta ja sinnikkyyttä. Sisarukseni Nina, Kati ja Pepe: ilman teitä en olisi se, joka nyt olen. Kiitos, että voin luottaa tukeenne. Aki, Raija, Miikka, Erja, Niko, Alisa, Ville, Katsu, Thomas, Nicole, Taika, Niko; kiitos, että olen saanut kokea iloa ja hauskuutta seurassanne, ja tutkimustyön rasitukset ovat välillä unohtuneet.

Lapseni, kaikkeni, Andrés, Roope, Sanawal – kiitän elämää, että saan olla teidän äitinne. Mikään ei ole tärkeämpää kuin olla äiti, mutta tiedätte, että minulla on tarve tehdä monenlaisia asioita. Koen, että olette sen hyväksyneet, kiitos rakkaat siitä. Neilikka, olen iloinen ja kiitollinen siitä, että olet tullut osaksi perhettämme.

Lopuksi lämmin kiitos puolisolleni, dosentti Jussi Karjalaiselle. Olet osana tutkimusryhmäämme ollut eteenpäin työntävä voima. Olet oman laajan tutkimustyökokemuksesi myötä tyynesti ottanut vastaan turhautumiseni ja auttanut hankaluuksissa. Kiitos loppumattomasta tuestasi ja rakkaudestasi.

Kangasalla 20.11.2023

ABSTRACT

Indoor air quality problems are considered important health risk worldwide and in Finland, they have caused public concern about permanent health deterioration. In epidemiological studies, it has been observed that indoor moisture damage (MD) exposure is associated with respiratory health effects, such as upper respiratory tract symptoms, the development of asthma and asthma deterioration. These studies have mainly focused on children's risk of asthma and other respiratory tract symptoms and on exposure at home or in schools. Some previous research has also established a temporal relationship between workplace MD exposure and asthma and rhinitis symptoms. However, due to a lack of clinical research, there has been a gap in knowledge at the individual level about the conditions and findings that underlie MD-associated symptoms when asthma, rhinosinusitis, or other symptom explanatory illnesses are not found.

The aim of this thesis was to describe the patient characteristics, the prevalence of different symptoms, and the clinical findings in secondary healthcare, among patients with workplace MD-associated respiratory tract or voice symptoms. The special interest was in improving the differential diagnostics among asthma, laryngeal findings, and multiple chemical sensitivity (MCS). Comprehensive clinical tests were used to diagnose respiratory tract illnesses. The findings of laboratory and allergy tests from the study patients were compared to those of the symptomless subjects. The frequency of MCS among the study patients was assessed with a questionnaire and compared to MCS prevalence in a control population randomly selected by the Finnish Population Information System.

The final study population consisted of 99 patients. Regarding workplace associated symptoms, 99% of the patients reported hoarseness or loss of voice, 85% reported a runny or stuffy nose, 92% reported coughing, and 86% reported dyspnoea. New-onset asthma with a temporal association with workplace MD exposure was diagnosed in one-third of the study patients. Laryngeal dysfunction was found in one-third and organic laryngeal changes in 22% of the patients, and these were common among patients both with and without asthma. Of the patients, 11% had chronic rhinosinusitis but none were diagnosed with acute bacterial rhinosinusitis.

Allergic sensitization was equally common in the study patients as in the 48 symptomless subjects. Minor clinically insignificant differences in blood counts were seen in the comparison between the study patients and the symptomless subjects. Among the study patients, elevated neutrophil counts were found in 19% with and 2% without asthma ($p=0.003$). The levels of CRP and ESR were low, and the study patients' FeNO, total IgE, and allergic sensitization were not increased compared to the symptomless subjects indicating a low probability of inflammatory processes or infections explaining the symptoms. Other serious illnesses such as hypersensitivity pneumonitis were not found.

The study patients had high scores significantly more often in chemical intolerance (39% vs. 23%, $p=0.001$) indicating a higher degree of MCS than among the population controls. Additionally, symptom severity (60% vs. 27%, $p < 0.001$) and life impact (53% vs. 20%, $p < 0.001$) with MCS were perceived as more significant among the study patients than among the population controls. Among the study patients, asthma, chronic rhinosinusitis, laryngeal problems, and allergic sensitization were not associated with the presence of MCS.

In conclusion, laryngeal findings were rather common among patients with workplace MD-associated respiratory tract or voice symptoms. Thus, proper differential diagnostics with lung function testing and investigations of the larynx and its function are recommended, in cases of prolonged workplace MD- associated respiratory tract or voice symptoms. Regarding upper respiratory tract symptoms, it is recommended to pay attention to the differential diagnosis between acute and chronic sinusitis. There were no basic laboratory or allergy test results characteristic of this patient group. However, inflammatory processes should still be excluded with basic laboratory tests, although the use of allergy tests does not seem necessary when the symptoms are clearly workplace associated. MCS was common among these patients, and it considerably affected their everyday life. MCS should be considered as a possible explanatory factor for MD-associated symptoms.

TIIVISTELMÄ

Sisäilmaongelmia pidetään maailmanlaajuisesti merkittävinä riskitekijöinä terveydelle, ja Suomessa ne ovat aiheuttaneet yleistä huolta terveyden pysyvästä heikkenemisestä. Epidemiologisissa tutkimuksissa on aiemmin havaittu, että altistuminen sisäilman kosteusvaurioille on yhteydessä hengityselinten terveysvaikutuksiin, kuten ylähengitysteiden oireisiin, astman kehittymiseen ja astman pahenemiseen. Tutkimustuloksia on pääasiassa liittyen lasten astmariskiin ja muihin hengitystieoireisiin ja kosteusvaurioaltistumiseen kotona tai koulussa. Joissain aiemmissa tutkimuksissa on myös löydetty ajallinen yhteys työpaikan kosteusvaurioaltistuksen, astman ja nuhaoireiden välillä. Kliinisen tutkimuksen vähäisyyden vuoksi ei kuitenkaan yksilötasolla ole ollut riittävää tietoa oireiden taustalla olevista löydöksistä, kun astmaa, poskiontelotulehdusta tai muuta oireita selittävää sairautta ei löydy.

Tämän väitöskirjan tarkoitus oli kuvata taustatekijöitä, eri oireiden esiintyvyyttä ja kliinisiä löydöksiä erikoissairaanhoidon diagnostiikassa potilailla, joilla oli työpaikan kosteusvaurioon liittyviä hengitystie- ja/tai äänioireita. Mielenkiinnon kohde oli erityisesti astman, kurkunpään toimintahäiriön ja monikemikaaliherkkyyden välisen erodiagnostiikan parantaminen. Hengitystiesairauksien diagnosoinnissa potilaille tehtiin kattavat kliiniset testit. Tutkimuspotilaiden laboratorio- ja allergiatestien tuloksia verrattiin oireettomien tuloksiin. Monikemikaaliherkkyyden esiintymistä tutkimuspotilailla arvioitiin kyselylomakkeella, ja tuloksia verrattiin Väestötietojärjestelmästä satunnaisesti valitun kontrolliväestön tuloksiin.

Tutkimuspotilaita oli 99. Työpaikkaan liittyvinä oireina 99 % potilaista ilmoitti äänen käheyden, 85 % vuotavan tai tukkoisen nenän, 92 % yskän ja 86 % hengenahdistuksen. Työpaikan kosteusvaurioaltistumiseen ajallisesti liittynyt astma diagnosoitiin kolmasosalla potilaista. Kurkunpään toimintahäiriöitä havaittiin 28 %:lla ja elimellisiä kurkunpään muutoksia 22 %:lla potilaista, ja nämä olivat yleisiä sekä astmaa sairastavilla että niillä, joilla astmaa ei todettu. 11 %:lla potilaista oli krooninen poskiontelotulehdus, mutta yhdelläkään ei todettu akuuttia bakteerin aiheuttamaa poskiontelotulehdusta.

Allerginen herkistyminen oli yhtä yleistä tutkimuspotilailla kuin 48 oireettomalla henkilöllä. Pieniä kliinisesti merkityksettömiä eroja veriarvoissa havaittiin verrattuna tutkimuspotilaiden ja oireettomien välillä, ja kohonnut neutrofiilisten valkosolujen määrä todettiin potilaista 19 %:lla, joilla oli astma ja 2 %:lla, joilla ei todettu astmaa (p=0,003). CRP-taso ja lasko olivat alhaiset, eivätkä tutkimuspotilaiden FeNO-arvot, kokonais-IgE-tasot tai allergisen herkistymisen yleisyys eronneet oireettomista. Näin ollen tulehdusprosessien tai infektioiden arvioitiin olevan epätodennäköisiä oireiden taustalla. Muita vakavia sairauksia, kuten allergista alveoliittia, ei potilailla todettu.

Tutkimuspotilailla oli merkitsevästi useammin monikemikaaliherkkyyttä kuin väestössä (39 % vs. 23 %, p = 0,001). Myös monikemikaaliherkkyyteen liittyvät oireet (60 % vs. 27 %, p < 0,001) ja niiden vaikutus elämään (53 % vs. 20 %, p < 0,001) koettiin merkittävämmiksi tutkimuspotilailla kuin väestössä. Tutkimuspotilailla astma, krooninen poskiontelotulehdus, kurkunpään ongelmat ja allerginen herkistyminen eivät olleet yhteydessä monikemikaaliherkkyyteen.

Johtopäätöksinä voidaan todeta, että kurkunpään löydökset olivat melko yleisiä tässä potilasryhmässä. Asianmukainen erotusdiagnostiikka keuhkojen toimintakokein sekä kurkunpään ja sen toiminnan tutkimuksin ovat siksi suositeltavia pitkittyneissä työpaikan kosteusvaurioon liitetyissä hengitystie- tai äänioireissa. Ylähengitysteiden oireiden osalta on hyvä kiinnittää huomiota erotusdiagnostiikkaan akuutin ja kroonisen poskiontelotulehduksen välillä. Tutkimuksessa ei havaittu tälle potilasryhmälle ominaisia laboratorio- tai allergiatestituloksia. Hengitysteiden tulehdukselliset sairaudet tulisi kuitenkin sulkea pois peruslaboratoriotutkimuksilla, mutta allergiatestien käyttö diagnostiikassa ei näytä tarpeelliselta, kun oireet liittyvät selvästi työpaikkaan. Monikemikaaliherkkyys oli potilailla yleistä, ja se vaikutti merkittävästi heidän jokapäiväiseen elämäänsä. Monikemikaaliherkkyyttä on syytä pitää yhtenä mahdollisena selittävänä tekijänä työpaikan kosteusvaurioon liittyvissä pitkittyneissä oireissa.

CONTENTS

ABBREVIATIONS

B-Eos	Blood eosinophil count
CBCT	Cone beam computed tomography
cfu	Colony forming unit(s)
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CRS	Chronic rhinosinusitis
ECP	Eosinophilic cationic protein
ESR	Erythrocyte sedimentation rate
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in one second
FIOH	Finnish Institute of Occupational Health
FVC	Forced vital capacity
Ig	Immunoglobulin (A, E, G, M)
IL-4, -6, -8	Interleukin-4, -6, -8
ILO	Inducible laryngeal obstruction
MCS	Multiple chemical sensitivity
MD	Moisture damage
MMVFs	Man-made vitreous fibres
MVOC	Microbial volatile organic compound
NO	Nitric oxide
ODTS	Organic dust toxic syndrome
OR	Odds ratio
ORL	Oto-rhino-laryngology
PEF	Peak expiratory flow
SPT	Skin prick testing
VCD	Vocal cord dysfunction
VOC	Volatile organic compound

ORIGINAL PUBLICATIONS

The thesis is based on the following original publications:

I Nynäs P, Vilpas S, Kankare E, Karjalainen J, Lehtimäki L, Numminen J, Tikkakoski A, Kleemola L, Uitti J. Observational cross-sectional study on Symptoms Associated to Moisture DAmage at Workplace: the SAMDAW study protocol. BMJ Open. 2019 Jun 25;9(6):e026485. doi: 10.1136/bmjopen-2018-026485

II Nynäs, P.; Vilpas, S.; Kankare, E.; Karjalainen, J.; Lehtimäki, L.; Numminen, J.; Tikkakoski, A.; Kleemola, L.; Uitti, J. Clinical Findings among Patients with Respiratory Symptoms Related to Moisture Damage Exposure at the Workplace—The SAMDAW Study. Healthcare 2021, 9, 1112. https://doi.org/10.3390/healthcare9091112

III Nynäs, P.; Vilpas, S.; Kankare, E.; Karjalainen, J.; Lehtimäki, L.; Numminen, J.; Tikkakoski, A.; Kleemola, L.; Uitti, J. Laboratory test results in patients with workplace moisture damage associated symptoms – the SAMDAW study. Healthcare 2023, 11, 971. https://doi.org/10.3390/healthcare11070971.

IV Nynäs, P.; Vilpas, S.; Kankare, E.; Karjalainen, J.; Lehtimäki, L.; Numminen, J.; Tikkakoski, A.; Kleemola, L.; Huhtala, H.; Uitti, J. Multiple Chemical Sensitivity in Patients Exposed to Moisture Damage at Work and in General Working-Age Population—The SAMDAW Study. Int. J. Environ. Res. Public Health 2021, 18, 12296. https://doi.org/10.3390/ ijerph182312296

AUTHOR CONTRIBUTIONS

The study design was planned by the author with the supervisor and the other authors. The author was responsible for patient recruitment, data collection, visualization, and writing the original drafts, as well as finalizing the articles. Funding acquisition, data curation, data analysis, and reviewing and editing of the articles were conducted by the author with the supervisor and the other authors.

1 INTRODUCTION

Indoor air quality problems are considered important risk factors for health worldwide (WHO, 2009). Indoor air associated symptoms may be interrelated with different indoor air quality problems, such as insufficient ventilation (Muscatiello et al., 2015), moisture damage (MD), unfavourable temperature conditions (Norbäck, 2009), dry indoor air (Wolkoff, 2018), dustiness (Schneider, 2008), and volatile organic compounds (VOC) (Salonen et al., 2009a). Respiratory symptoms or illnesses that have been demonstrated to be associated with indoor mould exposure include new-onset asthma, asthma deterioration, cough, wheezing, dyspnoea, rhinitis, and upper respiratory tract symptoms (Jaakkola et al., 2013; Mendell et al., 2011; Quansah et al., 2012), but the exact nature of exposure causing symptoms and illnesses is not known (WHO, 2009).

In epidemiological studies, workplace MD exposure has been shown to associate with development of asthma but evidence for a causal relationship has not been proven (Caillaud et al., 2018; Rollins et al., 2020) and upper respiratory tract symptoms (Wang et al., 2019). Some studies have described respiratory tract findings in patients having symptoms associated with MD exposure at work (Cox-Ganser et al., 2005; White et al., 2013), but previous research in this field has mainly been epidemiological (Mendell et al., 2011) and most of what is known concerns children's risk of developing symptoms in homes or schools with MD (Borràs-Santos et al., 2013; Karvonen et al., 2015). In most studies, the assessment of exposure to MD or the presence of symptoms or illnesses has been based on questionnaires (Kim et al., 2016; Kurth et al., 2017). Furthermore, only some subjects with MD exposure at the workplace are diagnosed with asthma (Karvala et al., 2011). In clinical experience, many patients with workplace MD exposure referred to secondary health care report intermittent hoarseness, loss of voice or difficulty inhaling, which would indicate functional or organic problems of the larynx.

Studies over the past decades have provided important information about environmental intolerance, in which a person has symptoms from different organ systems when in contact with an environmental factor that does not cause symptoms in most people (Genuis, 2013). In multiple chemical sensitivity (MCS), which is

considered a subtype of environmental intolerance, a person reacts with symptoms in association with low levels of airborne chemicals that most people tolerate without problems (Andersson et al., 2020; Dantoft et al., 2015). It seems that some proportion of the patients who have indoor air associated symptoms in fact have MCS, but the frequency of this condition among these patients is not known (Karvala et al., 2018).

The existing guidelines for examining patients with MD-associated symptoms are mainly based on studies of the health effects of MD exposure at home, and most of these studies have focused on children. The guidelines might not be ideal for examining adults exposed to MD at the workplace because exposure at work is different from that at home and usually lasts for a shorter time each day. In practice, routine allergy and laboratory tests are often used, but there is no evidence of whether they are effective for workplace MD-exposed patients with respiratory tract symptoms.

In Finland, due to commonly experienced indoor air associated symptoms and a growing public concern over MD in buildings and its possible permanent effects on occupants' health, the Prime Minister's office has set up established Healthy Premises 2028 project. Its objectives are to restore public buildings and increase the effectiveness of the treatment and rehabilitation of subjects with indoor air associated symptoms. The Finnish Institute for Health and Welfare is responsible for executing the project, which aims to enhance the understanding of the effects of indoor environments on health and well-being and to improve the treatment of people with symptoms and illnesses (Lampi et al., 2020).

Improvements in treatment and rehabilitation call for more knowledge about the individual level of the conditions and findings that underlie MD-associated symptoms, which is why an observational clinical study gathering information systematically was needed.

2 REVIEW OF THE LITERATURE

2.1 Indoor air associated symptoms

Since the 1970s, the symptoms and diseases caused by factors related to the indoor climate have become a significant challenge for occupational and environmental medicine in workplaces where the work itself does not involve significant exposure to dust, chemicals, or other industrial pollutants. Such workplaces are, for example, hospitals, day care centres, schools, and offices.

The term "sick building syndrome" began to be used for symptoms among occupants considered to be related to indoor air, specifically to air conditioning. In sick building syndrome, various symptoms that occupants had associated with indoor air included eye, skin, and upper airway irritation, headache, and fatigue (Finnegan et al., 1984). However, it was also found that the symptoms were related to non-building-related factors such as urban living and the psychosocial work environment (Norback and Edling, 1991). Symptoms were often found to be troublesome and limiting even when no physiological changes were observed (Redlich et al., 1997). Later, it was also noted that building repairs and improvements did not always bring health benefits (Park et al., 2018; Vornanen-Winqvist et al., 2018).

In surveys among employees of buildings where indoor air problems are experienced, 26-32% have had indoor air related symptoms (Lu et al., 2015; Magnavita, 2015). In Finland, based on a questionnaire answered in 1996-99 by 11 154 office employees of workplaces with suspected indoor air problems, up to 20% experienced workplace indoor air associated symptoms, most commonly upper respiratory tract and eye symptoms, and fatigue (Reijula and Sundman-Digert, 2004). In the same questionnaire in 2011–2012 and 2015–2017, of 28 826 employees in office, school and health care environments, up to 27% had indoor air associated symptoms, the most common symptoms being nasal and eye symptoms, and hoarse or dry throat (Tähtinen et al., 2020).

Indoor air associated symptoms are also experienced in buildings without obvious problems. In the OFFICAIR project of 11 European countries almost one

third of employees of newer (not in need of repair) office buildings had workplace associated symptoms, especially dry eyes and headache (Bluyssen et al., 2016).

Studies have found that women usually experience more indoor air associated symptoms than men in the same conditions (Lee et al., 2018; Magnavita, 2015). This phenomenon has not been satisfactorily explained by most occupational, building related, or personal factors (Brasche et al., 2001).

2.2 Possible causative factors of indoor air associated symptoms

In low-income countries, indoor use of fuels in cooking and heating causes the most harmful indoor air quality problems (Rosário Filho et al., 2021). In higher-income countries, moisture damage (MD) is considered the most important health affecting indoor air quality problem.

In Europe, North America, Australia, India and Japan, MD is estimated to affect 10-50% of indoor environments (WHO, 2009). However, indoor air quality is also affected by several other factors, such as ventilation, thermal conditions, cleaning quality, humidity, tobacco smoke, mineral fibres, material emissions and dust. In the workplace, respiratory symptoms could also be associated with perfumes, outdoor pollen, allergens of animal origin or houseplants.

Indoor air associated symptoms are not specific; i.e., it is usually not possible to deduce from the symptoms what might be causing them. Respiratory tract symptoms have been found to be connected not only to MD but also to ventilation (Sundell et al., 2011), indoor temperature (Azuma et al., 2018), humidity (Lukcso et al., 2016), volatile organic compounds (VOCs) (Lu et al., 2015), dustiness (Arikan et al., 2018), and man-made vitreous fibres (MMVFs)(Salonen et al., 2009b).

In addition, it has been found that psychosocial factors such as high levels of mental strain and stress at work can increase the experience of symptoms and harm associated with indoor air (Lahtinen et al., 2004; Runeson-Broberg and Norbäck, 2013).

2.2.1 Ventilation

It has been proposed that respiratory infections, asthma symptoms and short-term sick leaves can increase with lower ventilation levels (Sundell et al., 2011) and in

naturally ventilated (without mechanical ventilation) offices, the microbial concentrations might be higher than in mechanically ventilated or air-conditioned offices (Gołofit-Szymczak and Górny, 2018). Well-functioning ventilation should remove indoor air pollutants, such as respiratory pathogens (Wolkoff et al., 2021). Dutch intervention studies to improve ventilation indeed resulted in decreased levels of some indoor air pollutants (endotoxins, β(1,3)-glucan and particles with diameters of <10 μm) (Rosbach et al., 2016), particulate matter and black carbon (van der Zee et al., 2017). However, a Finnish study found that changes in ventilation that resulted in a decrease in VOCs, fine particulate matter, and indoor mycobiota did not significantly improve perceived indoor air quality (Vornanen-Winqvist et al., 2018). Conversely, some studies have observed better worker health and productivity (MacNaughton et al., 2015) and fewer indoor air associated symptoms (Sundell et al., 2011) in association with improved ventilation.

Ventilation systems might also be a source of indoor microbes, allergens and other pollutants if not properly maintained, thus increasing exposure (Nevalainen et al. 2015; Wolkoff et al., 2021).

2.2.2 Indoor temperature and humidity

Ventilation plays an important role in the regulation of indoor temperature and humidity at least in buildings with mechanical ventilation associated with workplace indoor air (Kielb et al., 2015). In buildings with MD, certain VOCs of bacterial and fungal origin have been detected. They have been considered to cause eye and upper airway irritation (Korpi et al., 2009). Higher indoor temperatures are associated with increased respiratory symptoms, and some studies have suggested that the threshold beyond which symptoms increase is between 26 °C and 32 °C (Tham et al., 2019). Women might be more sensitive to unpleasant thermal conditions than men (Karjalainen, 2012; Schellen et al., 2012). A recent review suggested that indoor temperatures between 22 °C and 24 °C could be most beneficial in terms of work performance (Wolkoff et al., 2021).

The perception of dry indoor air is associated with upper airway symptoms (Wolkoff, 2018), although the perception of dry indoor air is not always confirmed by measurements of true relative humidity (Järvi et al., 2018a). In a U.S. study of a government building complex with 7637 occupants, respiratory tract symptoms were associated with low relative humidity (measured relative humidity of 35-40%) and not with observed mould levels (Lukcso et al., 2016). It has been suggested that

relative humidity between 40% and 60% could be most beneficial to health and work performance (Wolkoff et al., 2021).

2.2.3 Volatile organic compounds

Volatile organic compounds (VOCs) are indoor air pollutants from diverse building materials, paints, cleaning agents, furnishings, and coverings (Kwon et al., 2018). In addition to building materials, VOCs in office environments are related to microbes (Choi et al., 2016) but also to different human actions (cleaning, cooking, smoking) (Abbatt and Wang, 2020) and outdoor environment (Choi et al., 2016). One VOC, 2-ethyl-1-hexanol, has been suspected of causing indoor air associated symptoms since it has caused irritation of the upper airways and eyes with inhalation exposure of experimental animals and human volunteers (Wakayama et al., 2019). Some researchers have presented VOCs as the cause of indoor air associated symptoms (Nakaoka et al., 2014; Takigawa et al., 2010), especially upper respiratory symptoms (Lu et al., 2015) even in air-conditioned offices with VOCs at less than the recommended levels (Azuma et al., 2018). Kwon et al. found an increase in the level of indoor VOCs, eye symptoms and the level of a xylene metabolite in inpatients, caregivers, and workers after a move to a newly built hospital, and the authors suggested that higher levels of VOCs could be associated with airway inflammation (Kwon et al., 2018). However, exposure to VOCs in office-like circumstances according to some researchers is too low to cause asthma, exacerbation of asthma or even irritation of mucous membranes (Kanchongkittiphon et al., 2015; Nurmatov et al., 2015; Wolkoff, 2013).

2.2.4 Dustiness and man-made vitreous fibres

Settled dust acts as a reservoir for moulds, allergens, and VOCs. Kielb et al. found that indoor air associated symptoms were associated with reported dustiness among teachers (Kielb et al., 2015). Different human actions in indoor spaces enhance the resuspension of dust (Lewis et al., 2018), causing irritation and allergic symptoms in some subjects (Arikan et al., 2018). More frequent vacuuming in offices could be associated with fewer general symptoms amongst the workers (Andersson et al., 1997; Korpi et al., 2009) especially in sensitive persons (Nakaoka et al., 2014). However, VOCs are not solely associated with MD and might also be associated with irritation symptoms also in new buildings (Skyberg et al., 2003; Suzuki et al.,

2021). In rooms with more dust, irritative agents such as fibres and formaldehyde, could be more abundant (Smedje and Norbäck, 2001). In a U.S. study of a large office complex, dust samples from 57 sample areas were investigated. The dust consisted mostly of desquamated skin cells, as well as fungal spores, fibrous glass particles, and other fibres (Lukcso et al., 2016).

MMVFs occur in building insulation materials, such as stone, glass, or mineral wools. Indoor fibre sources might include thermal insulation, sound and heat insulation of ventilation equipment, and acoustic ceiling boards. MMVFs have been suggested to cause irritation of the skin, eyes and upper airways (Salonen et al., 2009b) but not inflammatory responses (Paananen et al., 2004).

2.2.5 Emissions

Ozone has a strong oxidizing capacity and is considered an essential ambient air pollutant with cardiovascular and respiratory health effects (Hubbell et al., 2005). Its indoor sources are photocopiers, laser printers and other electronic devices such as room air purifiers (Guo et al., 2019). Ozone has been linked to respiratory health effects and its concentrations can be significant depending on the building circumstances (Salonen et al., 2018). Additionally, emissions of nanoparticles (Khatri et al., 2013) from printers and photocopiers are suspected to cause upper and lower respiratory symptoms. Other pollutants, such as aldehydes, nitric dioxide (NO2), particulate matter (PM2.5) (Sakellaris et al., 2021) and other oxidants (Abbatt and Wang, 2020) usually exist in workplace indoor air and could act as respiratory irritants. However, these emissions apparently act as significant indoor air pollutants primarily in newer airtight buildings designed to be energy conserving (Niculita-Hirzel, 2022) while significant MDs are more likely to occur in older buildings (Hägerhed-Engman et al., 2009; Norbäck et al., 2017; Reijula et al., 2012).

2.3 Building moisture damage

2.3.1 Occurrence

Visible mould identified by residents or moisture damage noted by an expert is common in buildings. In a survey in New Zealand, one-third of the respondents reported visible mould in their houses (Howden-Chapman et al., 2005). In a

Norwegian study, 10 000 houses were inspected by qualified building inspectors and MDs requiring further measures were found in 31% of the homes (Becher et al., 2017). In Finland, which is located in a subarctic area, approximately half of the private houses that were inspected by experts were estimated to be in need of repairs or further investigations in the 1990s (Nevalainen et al., 1998).

There have been different estimations of the prevalence of MDs in workplace buildings. The HITEA study assessed the occurrence of MD using questionnaires and inspections by trained research personnel in school buildings in the Netherlands, Spain, and Finland, representing different climatic regions. They concluded that the prevalence of MDs in school buildings is at least 20%, 41%, and 24%, respectively (Haverinen-Shaughnessy et al., 2012). In Finland, it has been assessed that 20–26% of hospitals and health care centres and 12–18% of schools and kindergartens have significant MD, whereas in office buildings, the respective proportion is estimated to be 2.5–5% (Reijula et al., 2012).

On average, MD has been estimated to exist in 33% of indoor spaces in Finnish public buildings (Annila et al., 2017). However, factors such as air leakage in structures, pressure differences across structures and ventilation affect how impurities spread into indoor air and possibly cause health effects. Different research methods, target buildings, and definitions of MD have varied across studies and comparison of the results are not always possible (Annila et al., 2017).

2.3.2 Exposure associated with moisture damage

There is no unanimous definition of MD, and researchers have used different terms, such as water damage or dampness, to describe the same problem: excess moisture in building structures resulting in microbial growth and degradation of the materials. In this study, the term moisture damage is used to represent this phenomenon in the sense that, e.g., transient water leakage does not lead to MD if properly repaired within a reasonable time.

Moisture is present to some extent in many building structures (Annila et al., 2017). Excess moisture (dampness) in structures is usually a consequence of water leakage and, if not repaired, results in fungal and bacterial growth and building structure degradation. Concentrations of culturable fungi in indoor air of dwellings worldwide are usually lower than concentrations outdoors. In office buildings, the concentrations are typically lower than in homes. The fungal species in MD can be the same as those regularly found indoors, but there are species that are usually found

only in MD (Adams et al., 2020). Common species in buildings with MD are, for example, Penicillium *spp.* and *Aspergillus* spp., as are *Chaetomium* spp., *Acremonium* spp., and *Ulocladium* spp. Different species typically exist on different building materials. For example, *Acremonium* spp. are typically found on gypsum, *Trichoderma* spp. on wood, and *Aspergillus fumigatus* on concrete (Andersen et al., 2011).

Spores and other biological and nonbiological particles transfer from damaged materials into indoor air by ventilation and mechanical disturbances. If there is a leakage route from the damaged structures indoor air can be contaminated by microbial spores and metabolic products, volatile organic compounds, and degradation products from the materials. Poorly balanced ventilation causing negative indoor pressure enhances the passage of impurities from structures into indoor air (Seppänen and Fisk, 2004). In addition to ventilation and the extent of MD, the concentration of culturable fungi in indoor air is also affected by human actions, humidity, and the climate (Nevalainen et al., 2015).

Different microbial products or components have been recognized in indoor air and dust in buildings with MD. More than 200 compounds are considered microbial volatile organic compounds (MVOCs) originating from microbial metabolism. Their concentrations in indoor air can be measured, but their presence does not readily demonstrate microbial growth since they are not always of microbial origin (Choi et al., 2016; Korpi et al., 2009). MVOCs are believed to explain the musty, basement-like smell in buildings with MD (Shinohara et al., 2018). Different fungal toxins, mycotoxins, are produced by fungi in secondary metabolism. They can be detected in indoor air and settled dust as well as in buildings without MD (Fromme et al., 2016).

The bacterial growth and survival of viruses can be enhanced by dampness (WHO, 2009). Bacterial bioaerosols are usually human-associated and their abundance can depend on ventilation (Meadow et al., 2014) rather than the structural features of buildings (Park et al., 2021). However, different Actinobacteria, such as *Streptomyces,* can grow on materials, especially if they are visibly mouldy (Rintala, 2011). Endotoxins are components of Gram-negative bacteria and can be found in indoor air associated with dust particles or aerosols (WH,O 2009).

In addition to different biocontaminants, degrading building materials are sources of indoor air impurities in MD. VOCs (Claeson et al., 2009), chloroanisoles (Gunschera et al., 2004), plasticizers (Kim et al., 2007), formaldehyde (Seguel et al., 2017), and other chemicals can complicate indoor air quality problems.

2.3.3 The significance of moisture damage exposure

Indoor MD exposure is also a mixture of different biological and nonbiological elements and their interactions (Nevalainen et al., 2015; Vornanen-Winqvist et al., 2020). Attempts have therefore been made to assess the harmfulness of indoor air by measuring the toxicity of indoor air particles. Toxicity testing was originally developed to test drugs before clinical testing in humans, and the purpose of the testing is to detect possible harmful effects on the target organism. Indoor air toxicity has been examined with the potential of, e.g., settled dust toxicity causing the death of human or bacterial cells or fruit flies. However, the development of useful toxicity tests requires understanding of the underlying causes and mechanisms of the symptoms associated with indoor air quality problems (Mahiout et al., 2019). Differences in toxicity between buildings with and without MD have not yet been detected (Tirkkonen et al., 2017). Overall, exposure in buildings with MD is a complex and poorly understood phenomenon (Gabrio and Weidner, 2018).

In Finland, updated guidance instructs (occupational health) doctors in the evaluation of the health significance of indoor air matters. If the moisture damage (in one or more parts of the building) is extensive, and there is an air connection to the working premises, and working in the premises is long lasting, there is believed to exist a health-based cause for building remediation. However, the guidance urges that MD be repaired primarily to maintain the conditions of the building and a good working environment (Reijula et al., 2022).

When assessing research on the health effects of MD, it must be considered that exposure at the workplace is different from that at home: less time is usually spent in the workplace than at home, children and pets are usually absent, and the premises, ventilation, and activities are different. Therefore, direct conclusions about MD-associated health effects assessed with studies of MD exposure at home cannot be drawn.

The possible mechanisms of MD exposure associated health effects are discussed in Section 2.4.6.

2.4 Moisture damage associated respiratory tract symptoms and diseases

Epidemiological studies have demonstrated associations between indoor MD exposure and health effects in different parts of the world: Europe (Järvi et al. 2018b;

Juel Holst et al., 2020; Wang et al., 2019), North America (Kielb et al., 2015; Kurth et al., 2017), Australia and Oceania (Ingham et al., 2019; Knibbs et al., 2018) and Asia (Cai et al., 2020; Saijo et al., 2010). Most of these studies concerned children's risk for respiratory symptoms and illnesses associated with MD exposure at home.

2.4.1 Respiratory tract symptoms in relation to moisture damage

In epidemiological studies, sufficient evidence of MD association with different respiratory tract symptoms such as dyspnoea, wheezing, coughing, respiratory infections, bronchitis, allergic rhinitis, and upper respiratory tract symptoms has been established (Mendell et al., 2011). A meta-analysis of eleven cross-sectional studies suggested that MD at schools is associated with a moderate increase in health risk, and the strongest risk was for coughing and wheezing, both in children and in adults (Fisk et al., 2019).

2.4.2 Rhinitis symptoms and sinusitis in association with moisture damage

In questionnaire studies assessing the risk for rhinitis symptoms related to MD, associations have been found between MD at home or the workplace and rhinitis symptoms or chronic rhinosinusitis (CRS) (Ahlroth Pind et al., 2017; Wang et al., 2019). In a review and meta-analysis on MD and upper respiratory symptoms, mould odour had the strongest association with rhinitis (effect estimate 2.18 (95% CI 1.76-2.71)) (Jaakkola et al., 2013).

In a Finnish clinical study including 28 patients with chronic hyperplastic sinusitis and MD exposure at home or work, differences in microbial findings were not found in nasal lavage fluid, tissue eosinophilia or earlier operations in patients and healthy controls. The authors concluded that MD exposure and chronic hyperplastic sinusitis or fungal sinusitis were not associated, and the fungal findings of the nasal cavity reflected environmental exposure (*Cladosporium* and *Alternaria*) (Kostamo et al., 2005).

In a study of occupants of severely moisture damaged homes, higher microbial levels in building materials were associated with increased upper respiratory symptom prevalence and worse perceived health (Järvi et al., 2018b).

Moisture damage in the workplace and rhinitis symptoms

In epidemiological studies, the association between workplace MD and rhinitis symptoms has been established to be somewhat elevated. In a North European study with 11506 respondents and a mean follow-up of 11 years, MD at the workplace was associated with rhinitis (OR 1.31 (95% CI 1.11-1.54)) (Wang et al., 2019). In a U.S. survey of 1100 teachers of 24 randomly selected schools, MD was associated with nasal congestion (OR 2.4 (95% CI 1.6-3.7)) (Claudio et al., 2016).

In a study of 153 office workers in which MD exposure was defined by fungal findings in vacuumed dust, MD was associated with nasal mucus excretion and nasal lavage inflammatory markers suggesting a nonallergic response to MD exposure (Akpinar-Elci et al., 2013).

2.4.3 Asthma

Asthma is a common airway disease with a prevalence of 4-21% (doctor-diagnosed asthma) in adults in different countries. Prevalence variations are largely explained by different definitions of asthma and available medical resources (To et al., 2012). In Finland, the prevalence of doctor-diagnosed asthma in surveys is approximately 11% (Hisinger-Mölkänen et al., 2019; Honkamäki et al., 2019).

Asthma is characterized by hyperresponsiveness and associated variable bronchoconstriction and chronic bronchial inflammation. Airflow limitation leads to wheezing and dyspnoea, and inflammation induces cough and mucus excretion. In mild or incipient asthma, symptoms are variable and lung function is normal most of the time. More severe or long-lasting inflammation can result in permanent mucosal changes. Several phenotypes of asthma with differences, e.g., in the type of bronchial inflammation, allergic sensitization, age at the onset of the disease, response to medication, and symptom presentation, have been reported (Asthma: Current Care Guidelines Abstract, 2022; Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2023). In most patients, asthma represents a type 2 inflammation characterized by eosinophilic mucosal inflammation often associated with elevated blood eosinophil counts, IgE levels, and nitric oxide levels in the exhaled air (Berry and Busse, 2016). Type 2 asthma is usually either childhood-onset allergic asthma or adult-onset eosinophilic asthma without allergies. Non-type 2 asthma often presents as late-onset asthma, obesity associated asthma, smoking associated asthma, or smooth muscle mediated asthma. The severity of the disease is not associated with the phenotype per se (Wenzel, 2012).

A Finnish 11-year follow-up postal survey concluded that an adult person's risk for asthma (effect estimate) was 2.19-fold greater (95% CI 1.49-3.22) if the person had a family history of asthma, 2-fold greater (95% CI 1.40-2.87) if the person had allergic rhinitis, and 2.06-fold greater (95% CI 1.35-3.16) if the person smoked. Among women, the asthma risk was 1.59-fold greater (95% CI 1.08-2.34) compared to men (Pallasaho et al., 2011). Certain occupations are associated with an increased risk of developing asthma. A historically well-known example of occupational asthma is baker's asthma caused by inhalation exposure to flour dust. In a Finnish registry-based study of data in 1986–1998, bakers' risk for asthma was 3.78-fold greater (95% CI 3.13–4.57) among men and 2.54-fold greater (95% CI 2.26–2.86) among women. Other occupations with more than a 2-fold risk for asthma were, e.g., laundry workers, shoemakers and repairers, tanners, metal plating and coating workers, railway and station personnel, and round-timber workers (Karjalainen A et al., 2002).

The prevalence of asthma has been increasing but the burden of asthma has been decreasing, as measured by hospitalizations, disability pensions and overall costs of asthma in Finland (Haahtela et al., 2017). Factors that have been linked with severe asthma include male sex, smoking, non-steroidal anti-inflammatory drug exacerbated respiratory disease, chronic comorbidities, two or more siblings (Toppila-Salmi et al., 2021), obesity (Barros et al., 2017), allergies, chronic obstructive pulmonary disease, anxiety and depression, dysfunctional breathing, vocal cord dysfunction, obstructive sleep apnoea, gastro-oesophageal reflux, and bronchiectasis (Porsbjerg et al., 2018).

Moisture damage and asthma

Related to MD exposure, the risk of asthma has been estimated to be somewhat increased. A WHO expert group concluded that there was sufficient evidence that MD in general was associated with new-onset asthma and asthma deterioration. Current asthma was assessed to be associated with MD in residences (WHO, 2009). Later, a review by Mendell et al. of epidemiological studies and meta-analyses stated that there was sufficient evidence that MD is associated with new-onset asthma and asthma deterioration in both allergic and nonallergic subjects (Mendell et al., 2011). A review of research from 2000 to 2013 concluded that there was sufficient evidence that outdoor fungi can cause asthma exacerbation in subjects sensitized to fungi and that MD can cause asthma in children (Kanchongkittiphon et al., 2015). Quansah et al. assessed the risk of asthma due to residential MD in their review and meta-

analysis. The risk for asthma was calculated to be 1.33-fold increased (95% CI 1.12–1.56) in association with MD, 1.29-fold increased (95% CI 1.04–1.60) in association with visible mould, and 1.73-fold increased (95% CI 1.19–2.50) in association with mould odour at home (Quansah et al., 2012).

Some studies have found the strongest association between MD and asthma in atopic subjects (Juel Holst et al., 2020), whereas other studies have found the same association in non-atopic subjects (Cox-Ganser et al., 2005; Graff et al., 2019).

Epidemiological studies on asthma associated with workplace moisture damage

Epidemiological studies conducted between 2006 and 2017 suggested that moisture damage in the workplace is associated with the onset and worsening of asthma (Caillaud et al., 2018). Based on recent questionnaire studies, MD in the workplace has been concluded to be temporally associated with asthma (Kurth et al., 2017; Rollins et al., 2020).

In a Finnish 3- to 12 -year follow-up of 483 subjects with asthma-like symptoms in association with workplace MD, a fourfold risk of self-reported asthma with continuous MD exposure was observed (Karvala et al., 2011). In a ten-year follow-up study of 11506 adults from Iceland, Norway, Sweden, Denmark and Estonia, workplace MD was associated with the onset of self-reported asthma (Wang et al., 2019). In the same study, among subjects with self-reported MD in the workplace building, the risk for doctor-diagnosed asthma was somewhat elevated with odds ratio (OR) being 1.40 (95% CI 1.10-1.79). Mould odour at home was the factor most distinctly correlated with asthma with OR 2.23 (95% CI 1.48-3.37) (Wang et al., 2019). In a Swedish 20-year retrospective study of 222 subjects with self-reported MDs in the workplace, 10 new self-reported asthma cases were detected. The incidence rate ratio of asthma was non-significantly elevated, at 2.3 (95% CI 0.8-6.8) (Graff et al., 2019).

It would be reasonable to expect remediation of MD to relieve occupants' symptoms. According to the Cochrane review by Sauni et al., MD remediation was concluded to reduce asthma-related symptoms, the use of asthma-medication and respiratory infections (Sauni et al., 2011). However, no such relief was found during a 7-year follow-up of more than 1000 employees in an office building with several remediation projects (Park et al., 2018).

Clinical studies on asthma associated with workplace moisture damage

Few studies have conducted clinical tests assessing respiratory tract function in association with workplace MD. In a study of employees working in an office building with MD in the U.S., adult-onset asthma prevalence confirmed by spirometry and methacholine challenge tests was 12% (103 asthma cases among 865 employees) (Cox-Ganser et al., 2005). White et al. described serial peak expiratory flow (PEF) findings among 22 employees from an office building with MD. Serial PEF measurements with acceptable quality were performed by 14, of whom five had work-related PEF changes. Of these five, three reported having asthma (White et al., 2013).

Iossifova et al. reported the development of abnormal forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and methacholine challenge test findings in 97 employees from an office building with ongoing MD remediation over three years. In the first examinations, 18 cases of post-occupancy related asthma were detected. Three years later, three of these cases reported no longer having current asthma (Iossifova et al., 2011).

Hyvönen et al. described a cluster of asthma cases in a Finnish workplace building under remediation due to significant MD, technical deficiencies, and ventilation problems. Among 290 workers in the building, new-onset asthma was diagnosed in 21 workers (7.2%) during the 8-month renovation period with dust suspended in the indoor air (Hyvönen and Syrjälä, 2019).

These studies practically demonstrate that asthma can be found among some subjects with symptoms associated with workplace MD. However, the other possible reasons for a subject developing asthma, e.g., allergic sensitization, were not sufficiently discussed. Additionally, when studying subjects from real-life workplaces the exposure is not homogenous; at least two of the workplace buildings from the previously presented studies were under reconstruction which means that the employees were exposed to renovation dust that can be irritating to the respiratory tract (Hyvönen and Syrjälä, 2019; Iossifova et al., 2011). In conclusion, although this type of study setting could appear best for demonstrating asthma risk associated with MD the results must be interpreted judiciously.

2.4.4 Laryngeal and voice symptoms

Symptoms related to breathing and coughing are not always asthma or lung related. Irritable larynx is a term referring to a hyperreactive larynx leading to increased muscle tension in the laryngeal muscles, dyspnoea due to laryngeal constriction, coughing and voice problems (Morrison et al., 1999). Of the work associated factors, irritants (Hoy et al., 2010) and frequent use of the voice (Denton and Hoy, 2020) are considered possible causes of irritable larynx . The proposed mechanisms for irritable larynx include central neuronal network plasticity after exposure, viral infection, inflammation due to e.g., gastroesophageal reflux and psychological factors (Anderson, 2015).

Vocal cord dysfunction (VCD) refers to a transient condition with inappropriate adduction of the vocal cords during breathing (Dunn et al., 2015). Cummings et al. described two cases of VCD temporally associated with working in an office with MD. The patients suffered from coughing, chest tightness, dyspnoea, wheezing, and hoarseness. Their spirometries were normal, and methacholine challenge tests did not show bronchial hyperreactivity excluding asthma with high a probability (Cummings et al., 2013).

The preferred term to describe laryngeal obstructions causing breathing problems is inducible laryngeal obstruction (ILO), including constriction at a supraglottic level (Christensen et al., 2015). Occupational or environmental irritants are considered possible causes of ILO, although there is no evidence of true irritant exposure in association with it. A possible mechanism of ILO, in addition to irritation related inflammation, is altered reflex sensitivity, which is potentially affected by psychological factors (Halvorsen et al., 2017).

Of individual professional groups, teachers' voice problems have interested researchers. It has been established that a tired or strained voice or hoarseness could be associated with indoor air quality problems among teachers (Vertanen-Greis et al., 2020a). Conversely, voice problems among them might also be associated with self-reported stress (Vertanen-Greis et al., 2020b) or other individual factors such as job dissatisfaction (Trinite, 2017).

2.4.5 Hypersensitivity pneumonitis and organic dust toxic syndrome

Hypersensitivity pneumonitis (HP; extrinsic allergic alveolitis) is a rare inflammatory disease of the small airways, alveoli, and surrounding lung interstitial tissue. It presents with coughing, dyspnoea, and general symptoms such as fever after

exposure. Environmental exposures that have been described as possible causes of HP include bacteria, fungi, animal proteins, plant proteins, low molecular weight chemicals, and metals (Raghu et al., 2020). Case reports of HP in association with MD exposure in home environments have been published (Dickson and Tankersley, 2015; Temprano et al., 2007). However, exposure to a possible causative agent of HP is not always recognized, and a potential intrinsic form of the disease has been proposed (Borchers et al., 2017; Raghu et al., 2020).

The classic case of HP is farmer's lung, caused by microbes in the hay and straw that are handled and spread in barns. Based on the Finnish Register of Occupational Diseases, e.g. in 2018, 14 cases of HP were diagnosed as an occupational disease in Finland (Koskela et al., 2018). All these cases were in farmers (Koskela Kirsi, oral communication).

Organic dust toxic syndrome (ODTS) is a self-limited, flu-like, transient febrile syndrome with symptoms in both the upper and lower respiratory tracts. It is considered a toxic reaction to organic dust and is usually seen in farmers after a major exposure to bioaerosols (Seifert et al., 2003). It was also earlier suggested to occur among subjects exposed to MD (Reijula, 1998). Leucocytosis and neutrophilia can be found with chest imaging and lung function tests remaining normal, differentiating the condition from HP (Institute of Medicine (U.S.). Committee on Damp Indoor Spaces and Health. 2004).

Hypersensitivity pneumonitis and organic dust toxic syndrome in association with workplace moisture damage

Suspicion of workplace MD exposure as a causative factor of HP is based on case reports (Eerikäinen et al., 2013; Kerätär and Reijula, 1995; Weltermann et al., 1998). In a U.S. study of 97 employees from a building with MD, four cases of HP were reported. However, it remains unclear whether measurement of diffusion capacity, (high resolution) computed tomography, or bronchoscopy was performed to confirm the diagnosis in this study (Iossifova et al., 2011). In a Finnish study of 14 employees from a building with MD, one was diagnosed with HP based on impaired diffusion capacity and typical findings on bronchoscopy (Seuri et al., 2000).

Since diagnosing HP is challenging, considering missing data from the cases, it is difficult to draw a conclusion about the association of HP with workplace MD (Raghu et al., 2020). Furthermore, the microbial exposure levels in office-like environments with MD are clearly lower than exposures through work including handling of polluted materials or environmental sources of major exposure such as

in farming (10^4-10^7 cfu/m^3) (Kotimaa et al., 1987). In the study of Salonen et al., the concentration range of airborne fungi was for buildings with MD (2–2470 cfu/m^3), but only approximately 20% of the samples exceeded 10^2 cfu/m^3 (Salonen et al., 2007).

Although many subjects exposed to MD experience symptoms that could be interpreted as ODTS, it is not considered probable among subjects with MD exposure in office-like environments where the concentrations of organic dusts are much lower than in occupations in which the condition is more common (Institute of Medicine (U.S.). Committee on Damp Indoor Spaces and Health. 2004). Exposure levels causing ODTS have been assessed to likely exceed 10^7 cfu/m^3 (Borchers et al., 2017).

2.4.6 Possible mechanisms of moisture damage associated symptoms and diseases

The estimates of the mechanisms of the health effects of MD exposure are largely based on studies at the cellular level (in vitro studies) and experimental animal models. In these study settings, microbial exposure was controlled and directed to target cells or organs at much higher concentrations than in indoor air. Based on this type of study, it is therefore not possible to draw conclusions about the mechanisms of health effects in the human body, in which the processing and metabolism of foreign substances are complex (WHO, 2009).

Irritation

Upper respiratory tract, eye and skin irritation is often associated with workplace indoor air (Kielb et al., 2015). In buildings with MD, certain VOCs of bacterial and fungal origin have been detected. They have been considered to cause eye and upper airway irritation (Andersson et al., 1997; Korpi et al., 2009) especially in sensitive persons (Nakaoka et al., 2014). However, VOCs are not solely associated with MD and might also be associated with irritation symptoms also in new buildings (Suzuki et al., 2021). Additionally, microbial spores have been considered irritating (WHO, 2009).

Immunological responses

Inflammatory responses to moulds have been demonstrated in mouse macrophages and bone marrow derived dendritic cells (Hirvonen et al., 1997; Vincent et al., 2017). In children with MD exposure at home, some studies have detected systemic inflammatory responses (increased levels of C-reactive protein (CRP), interleukin-1β (IL-1β) and tumour necrosis factor α (TNF-α) in serum and leucocytes in blood) but the research results have not been consistent (Järvi et al., 2018b; Karvonen et al., 2018; Mustonen et al., 2016).

Workplace MD and immunological responses

Since upper respiratory tract symptoms are common in association with MD, some studies have examined nasal mucosal cell and cytokine responses using nasal lavage fluid. They have shown different and somewhat contradictory responses based on levels of e.g., TNF-α, IL-4, -6 and -8, nitric oxide, eosinophilic cationic protein (ECP), myeloperoxidase, and neutrophils in nasal lavage fluid from workers exposed to MD (Akpinar-Elci et al., 2013; Hellgren et al., 2009; Hirvonen et al., 1999; Roponen et al., 2013; Wåhlén et al., 2016).

Previous research has also attempted to demonstrate systemic inflammation in workers exposed to MD. In a study of 82 patients examined because of symptoms associated with MD in homes or workplaces, increased levels of lymphocytes in bronchoalveolar lavage fluid and decreased levels of CD19 cells in blood were considered to suggest an active immune response in the lungs (Wolff et al., 2009).

Atosuo et al. postulated that exposure to microbial material results in immune system activation and the formation of specific immunoglobulins (Ig). They found elevated levels of IgG, IgG1 and IgG3 against *Streptomyces albus* and *Aspergillus versicolor* in workers from buildings with moisture damage, while IgA and IgM levels remained at the same level as in subjects from reference buildings. However, as the authors also admitted, IgG levels might correlate with exposure but not with symptoms (Atosuo et al., 2020). This phenomenon is previously known, and the analysis of mould specific IgGs has been used to demonstrate exposure in HP diagnostics (Selman et al., 2012).

In 62 employees of Swedish day care centres, the amount of fungal DNA in settled dust was associated with fractional exhaled nitric oxide (FeNO) and serum levels of CRP (which was, however, more closely associated with body mass index) (Norbäck et al., 2016). A Swedish study with a ten-year follow-up in a random sample

of 429 adults observed that blood eosinophils (B-eos) and ECP were associated with workplace MD at baseline, but not after follow-up (Zhang et al., 2012).

Among teachers with and without symptoms in schools with MD and reference schools, gene expression markers that could prove the development of immune system responses were identified by Ndika et al. However, in nasal epithelial cell or blood mononuclear cell samples, transcriptome profiles did not significantly differ depending on the building or symptom status. The results raised doubts regarding whether the symptoms related to MD have an organic background (Ndika et al., 2018).

IgE mediated sensitization

The most common outdoor mould species are *Cladosporium* spp. and *Alternaria* spp. (Prester, 2011). Reijula et al. studied the prevalence of IgE mediated allergies to *Alternaria alternata* and *Cladosporium herbarum* in Finland and discovered them to be rare, at 2.8% and 2.7%, respectively (Reijula et al., 2003).

In building structures and surfaces with MD, different potentially sensitizing mould species, such as *Penicillium* spp. and *Aspergillus* spp., are found (Andersen et al., 2011). Vincent et al. investigated whether mould exposure and specific IgE sensitization were associated with the severity of asthma. They concluded that sensitization to moulds is not linked to severe asthma but exposure to *Penicillium* spp. and *Aspergillus fumigatus* at home possibly is (Vincent et al., 2018). Conversely, it has been observed that living in farming environment with abundant fungal and mite exposure protects against allergic diseases (Campbell et al., 2017).

Aspergillus fumigatus, a frequently found fungal species in building structures with MD, is an easily sporulating fungus found abundantly in the soil (Latgé, 1999). Sensitization to *Aspergillus fumigatus* is linked to severe asthma (Denning et al., 2014; Vincent et al., 2018) but the fungus is commonly found in the airways of patients with asthma, regardless of the severity of their disease (Sullivan et al., 2019). There is evidence that sensitization to *Aspergillus fumigatus* in individuals with asthma becomes more prevalent with increasing age (Watai et al., 2018). In a study of 21- to 63-year-olds with recently diagnosed asthma in Finland, the prevalence of serum IgE antibodies against *Aspergillus fumigatus* was 5% in asthma patients and 2% in population controls (OR 2.73, 95% CI 1.38-5.40) (Jaakkola et al., 2006). In another Finnish study, in which the mean age of the participants with asthma was 59 years, 11% of the asthma patients and 4% of the population controls had SPT positive reactions to *Aspergillus fumigatus* ($p<0.001$) (Karjalainen J et al., 2002).

Regarding the mechanism of health effects, some studies have found evidence of IgE-mediated allergy to indoor moulds (Vincent et al., 2018), but others have referred to non-allergic mechanisms (Bornehag et al., 2004; Cox-Ganser, 2015). Using a nasal provocation test with commercial fungal allergens, 56 Finnish cases of occupational rhinitis were assessed. In 23% of the patients, IgE-mediated allergy to moulds could be established, most commonly to *Aspergillus fumigatus* (Karvala et al., 2008).

Borchers et al. speculated that, even if mould species are abundant, many of them are unidentified, and possibilities to test for sensitization do not exist even for all species that have been recognized (Borchers et al., 2017). However, association is not the same thing as causality, especially since the development of asthma is not fully understood (Portnoy et al., 2008). Sensitization shown with allergen specific IgE or a positive skin prick test does not necessarily indicate a disease; diagnosis of a clinical allergy also presumes symptoms in relation to allergen exposure (Heinzerling et al., 2013).

House dust mite allergens have been considered essential in MD-associated health effects (WHO, 2009). However, house dust mites and storage mites have been found in workplaces and homes both with and without MD (Koistinen et al., 2006; Pennanen, 2011) and they seem to be present in our environments perhaps more widely than usually thought, even in cereal products (Korsgaard and Harving, 2005; Thind and Clarke, 2001). Overall, the role of mite allergy in MD-associated health effects has not been proven (Bornehag et al., 2004). Mite sensitization has been assessed to have little independent association with asthma in Finland (Toppila-Salmi et al., 2015).

According to some studies, environmental allergens, such as pollen (Menzel et al., 2017) and animal dander (Sander et al., 2018), could play a role in indoor air associated symptoms among sensitized subjects.

Indoor air toxicity as a proposed mechanism of health effects

Some mould species produce mycotoxins in their metabolism, and ingested mycotoxins in mould infested products are known to cause adverse health effects (Magan, 2006). Mycotoxins have also been discovered in indoor environments of buildings with MD but the concentrations have been low (Fromme et al., 2016). According to some researchers, the toxicity of indoor aerosols demonstrated in vitro is an indicator of possible health effects (Andersson et al., 2010). However, the toxicity discovered in in vitro cell tests does not prove that mycotoxins occurring in

indoor air are able to cause health effects in the human body with its complex metabolism.

2.5 Psychosocial, cognitive, and personal factors affecting indoor air associated symptoms

In addition to building-related factors, workplace indoor air associated symptoms have been attributed to psychosocial and cognitive factors, such as finding the work interesting, the amount of work, the possibility of influencing working conditions, getting help from fellow workers (Lahtinen et al., 2004), low social support (Lu et al., 2018; Runeson-Broberg and Norbäck, 2013), interpersonal conflicts (Azuma et al., 2015), work strain (Magnavita, 2015; Thach et al., 2020), and the experience of injustice (Finell and Seppälä, 2018). Additionally, personal factors such as anxiety and depression (Magnavita, 2015; Runeson et al., 2004) could have an influence on experiencing indoor air associated symptoms. Conversely, working in a "known to be sick" building can induce psychological distress (Bauer et al., 1992).

Psychosocial stressors have also been shown to be associated with a systemic inflammatory response (Rohleder, 2014). In an Israeli study based on periodical employee check-ups, CRP and fibrinogen levels were associated with burnout in women, and depression in men (Toker et al., 2005). In a study of schoolteachers in Germany and Luxembourg, elevated TNF-α levels and decreased levels of IL-4 were associated with burnout symptoms (von Känel et al., 2008). Among these teachers, effort–reward-imbalance, analysed according to Siegrist's model, was associated with elevated TNF-α levels (Bellingrath et al., 2010).

2.6 Multiple chemical sensitivity

2.6.1 Definition

Multiple chemical sensitivity (MCS) (or chemical/odour intolerance) is a condition characterized by symptoms of different organ systems in association with low-level chemical exposure that is less than known harm-causing levels and does not cause symptoms in most people (Andersson et al., 2016). MCS is a subtype of environmental intolerance (Haanes et al., 2020), which includes reacting to different

environmental factors such as chemicals or odours, electromagnetic fields (Rubin et al., 2009), noise (Baliatsas et al., 2016) or buildings the person considers "sick" (Karvala et al., 2018).

A consensus in 1999 set six different criteria for a diagnosis of MCS: the condition is chronic; the symptoms are reproducible; and the symptoms appear in multiple organ systems, occur in response to low-level exposure to different chemicals, and resolve after exposure ceases (Bartha et al., 1999). Later, Lacour et al. emphasized the presence of central nervous system symptoms (Lacour et al., 2005).

2.6.2 Possible mechanisms

Environmental intolerance symptoms cannot be explained by any known toxicological (Hetherington and Battershill, 2013), physical (Schmiedchen et al., 2019) or immunological (Claeson and Andersson, 2017; Dantoft et al., 2015) mechanisms. Recent studies have suggested that the key mechanisms causing environmental intolerance could be central sensitization and changes in the neurological processing of sensory stimuli (Nordin, 2020; Tran et al., 2017; Viziano et al., 2018). In previous studies, odour detection or identification levels were not different between subjects with MCS and controls. However, brain responses have been stronger, and the perceived intensity and offensiveness of odours have been higher in subjects with MCS (Azuma et al., 2019).

2.6.3 Identification and prevalence

Since there is no recognized biological mechanism explaining MCS, there are no clinical tests for the diagnosis. To screen for the presence of MCS, different questionnaires have been developed (Andersson et al., 2009; Bailer et al., 2006; Haumann et al., 2003; Szarek et al., 1997) of which the Quick Environmental Exposure and Sensitivity Inventory (QEESI) (Miller and Prihoda, 1999) seems to be the most widely used (Alobid et al., 2014; Heinonen-Guzejev et al., 2012; Heo et al., 2017; Hojo et al., 2019; Jeong et al., 2014; Nordin and Andersson, 2010; Skovbjerg et al., 2012). However, there are still no commonly accepted definitions or diagnostic criteria for MCS (Palmquist, 2019). Some studies have distinguished between "doctor-diagnosed" and "self-reported" MCS and have shown different prevalence rates for these two phenomena. Epidemiological studies of self-reported MSC over the last decade have presented a prevalence between 3% and 26%, which is often

higher in women than in men (Heo et al., 2017; Skovbjerg et al. 2015). Women reporting more MCS could be linked to, e.g., women having a more sensitive olfactory function (Kobal et al., 2000) or being more worried about the possible health effects of environmental factors (Dömötör et al., 2019).

2.6.4 Treatment and prognosis

MCS can significantly affect the quality of the subjects' social and occupational lives (Alobid et al., 2014; Driesen et al., 2020). Mindfulness-based cognitive therapy (Hauge et al., 2015), cognitive behavioural therapy (CBT), and psychoeducation (Selinheimo et al., 2020) have not yet proven to be efficient treatment choices in MCS, which might partly be explained by psychopathology and other functional somatic disorders that previous studies have linked with MCS/environmental intolerance (Jimenez et al., 2019; Palmquist, 2017).

Recent research has suggested that MCS perhaps is not as permanent a condition as previously believed (Bailer et al., 2007; Ternesten-Hasseús, 2016). Palmquist reported 44% of subjects with specific environmental intolerance recovering over a six-year follow-up. In contrast, there was a 13% probability that a certain environmental intolerance would spread to another type of environmental intolerance (Palmquist, 2017). Azuma et al. identified improvement in 68% of 735 MCS cases in a five-year follow-up. Factors promoting improvement of MCS were physical activity and a regular lifestyle, including diet and sleep (Azuma et al., 2019).

2.6.5 Relation to indoor air quality problems

Nonspecific building-related symptoms (formerly sick building syndrome) refer to symptoms that a person attributes to certain buildings in which evidence of true indoor air quality problems is weak or non-existent. Nonspecific building-related symptoms and MCS likely share mechanisms (Nordin, 2020). Like MCS, nonspecific building-related symptoms could lead to avoidance behaviour and considerably affect the afflicted person's life (Karvala et al., 2018; Söderholm et al., 2016).

2.7 Examination of a patient with moisture damage associated symptoms

2.7.1 Finnish guidelines

Majvik and following recommendations

The first Finnish guidelines for examining patients with MD-associated symptoms were presented in Majvik's 1998 and 2006 recommendations (Nordman et al., 2007). It was then concluded that respiratory diseases caused by MD microbes include hypersensitivity rhinitis, asthma, HP, and ODTS.

When workplace associated symptoms were suspected, it was recommended to diagnose possible infections with necessary laboratory tests, and allergies with SPTs. A diagnosis of occupational rhinitis caused by workplace MD exposure required the demonstration of blood specific IgE antibodies, and provocation tests with the microbial extract. Occupational asthma diagnosis required positive findings with either serial PEF or specific bronchial inhalation exposure tests.

The practice to diagnose occupational asthma since 2009

According to the Finnish legislation, patients who are diagnosed with an occupational disease are entitled to reimbursement from their employers' compulsory insurance (Työtapaturma- ja ammattitautilaki 24.4.2015/459 (The work accident and occupational disease act) 2015). To establish occupational asthma diagnosis, a causal connection between the exposure and the disease must be demonstrated. In 2009, it was a consensus that the nature of the exposure in association with MD had remained unclear. Additionally, in MD associated asthma, IgE mediated sensitization to microbes was rare. Thus, the new agreed practice to demonstrate the causal connection was through PEF workplace (at and off work) monitoring (Lindström et al., 2009).

Current guidelines

The current Finnish guidelines (2017) for examining patients with symptoms associated with MD concluded that there was reasonable scientific evidence of upper respiratory tract symptoms, cough, wheezing, dyspnoea, new-onset asthma, and

respiratory tract symptoms of subjects with asthma being associated with MD exposure (Patient exposed to moisture damage: Current Care Guideline Abstract, 2017). Weak evidence was found for respiratory tract infections, and allergic rhinitis being associated with MDs. The working group concluded that there was no evidence of HP or ODTS being associated with MD exposure. The conclusions also mentioned that it had not been possible to establish a causal relationship between MD and any of the health effects since it is not known which factors cause the health effects and by what mechanism.

The guidelines instruct doctors to examine patients according to the symptoms that they present following general diagnostic recommendations. The Finnish current care guidelines on the diagnostics and treatment of asthma (Asthma: Current Care Guidelines Abstract, 2022), lower respiratory infections (Lower Respiratory Tract Infections (Adults): Current Care Cuidelines Abstract, 2015), and rhinosinusitis (Rhinosinusitis, Current Care Cuidelines Abstract, 2018) are recommended. No laboratory tests are considered to prove a connection between MD exposure and symptoms or illnesses. Skin prick tests or allergen specific IgE measurements are often used in patients with respiratory symptoms because atopy is a known risk factor and a phenotypic feature of many known respiratory diseases. Specific IgE antibody tests for moulds are not recommended in primary healthcare, and in secondary health care they are usually considered necessary only for patients with severe symptoms that suggest allergies or asthma. The development of HP caused by MD exposure was considered unlikely, but assessment in secondary health care is required to confirm any suspicion.

The guidelines also briefly address environmental intolerance in this context. The working group concluded that there is no research evidence that exposure to MD leads to the development of environmental intolerance. In 2015, subclass R68.81 ("Continuous or repeated exceptional sensitivity to normal environmental factors") was added to the Finnish ICD-10 classification. The introduction of the disease code was expected to promote the referral of patients to treatment, as well as statistics and research on environmental intolerance.

The (occupational health) doctor should encourage employers to order building structural and indoor air investigations if MD is suspected. (Patient exposed to moisture damage: Current Care Guideline Abstract, 2017)

2.7.2 Other guidelines

The German-Austrian Guidelines for Medical Diagnostics of Indoor Mould Exposure (2016) state that mould exposure can cause mucosal irritation, odour nuisance, and general malaise (Hurraß et al., 2017). Allergic respiratory diseases, asthma (manifestation, progression, exacerbation), allergic rhinitis, HP and respiratory tract infections/bronchitis are considered possible MD-associated diseases. According to the working group's interpretation, no causal relationship has been established between MD exposure and any disease. One possible explanation for the malaise associated with MD exposure is considered stress associated with adverse environmental exposure.

If an association between mould exposure and health effects is suspected, the medical diagnosis is recommended to include the medical history, physical examination, conventional allergy diagnostics, and if indicated, provocation tests. Doctors are encouraged to assess family medical history regarding allergies (even if the significance of predisposition to allergies in MD-associated symptoms is unclear). The authors concluded that indoor moulds could cause allergic sensitization, but not as often as other environmental allergens, and it is difficult to prove on an individual level anyway. The authors discussed the usefulness of determination of mould specific IgG, eosinophilic cationic protein, immune complexes, and serological determination of mycotoxins, among other things, and concluded that they are not of clinical value. Serological determination of galactomannan (of the cell wall of *Aspergillus*) and (1 → 3)-β-d-glucan can be used in the diagnostics of invasive mycoses but not in connection with indoor MD exposure. The guidelines recommend a holistic approach also recognizing the psychosocial aspects of health problems since environmental concerns and anxiety can affect well-being. (Hurraß et al., 2017)

3 AIMS OF THE STUDY

The focus of this thesis was to describe the patient characteristics, the prevalence of different symptoms, and the clinical findings in secondary healthcare, among patients with workplace MD- associated respiratory tract or voice symptoms. The specific aims were to

1) describe the patient characteristics, the prevalence of different symptoms, and the clinical findings;

2) determine the prevalence of laryngeal symptoms and findings and their co-occurrence with asthma;

3) explore the prevalence of multiple chemical sensitivity and whether it would explain the symptoms; and

4) determine whether it would be possible to allocate the clinical tests needed according to the patient's symptoms.

4 MATERIALS AND METHODS

4.1 Data collection

This thesis is based on four studies. The first study described the whole study protocol. Studies II and III were clinical descriptive studies, and study IV was a questionnaire study. The study design and populations used in analyses are presented in Figure 1.

Figure 1. Summary of the study design and populations used in analyses.

Study I		
Aims	To describe the whole study protocol	

Study II		
Materials	Patients (n=99)	Non-participants (n=28)
Methods	Clinical examinations according to the study protocol	Patient records
Aims	To describe the patient characteristics, the prevalence of different symptoms, the clinical findings, and the diseases; To control for possible bias related to willingness to participate	

Study III		
Materials	Patients (n=99)	Healthy controls (n=48)
Methods	Laboratory and allergy tests	Laboratory and allergy tests
Aims	To examine laboratory and allergy test findings in the patients; To find out if the findings of the patients were different than of healthy controls	

Study IV		
Materials	Patients (n=99)	Population controls (n=568)
Methods	QEESI questionnaire	QEESI questionnaire
Aims	To find out the prevalence of multiple chemical sensitivity; To find out if multiple chemical sensitivity was more common among the patients than in population	

4.2 Study populations

4.2.1 Patients (Studies II-IV)

The study was conducted at Tampere University Hospital, a secondary level referral centre for a population of 530 000 and a tertiary level referral centre for a population of approximately 1 million people. Patients referred to departments of Occupational Medicine or Phoniatrics or Allergy Centre because of symptoms associated with indoor complaints at their workplace were interviewed as possible study subjects. The study inclusion criteria were: 1) age between 18 and 65 years; 2) upper and/or lower respiratory tract and/or voice symptoms; 3) symptoms associated with the workplace; and 4) a strong suspicion of MD at the workplace (Table 1).

Table 1. The criteria on which moisture damage (MD) at the workplace was suspected (Ministry of Social Affairs and Health, 2009).

1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant
2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials, disengaging or blistering of flooring materials, crumbling of wall plastering, water leakages through ceilings (buckets on the floors), loose water on surfaces
3. Renovations because of MDs previously performed in the building
4. Information about MD findings from employer or occupational and health safety personnel

The exclusion criteria were: 1) severe illness (e.g., cancer); and 2) pregnancy.

After the study subjects had provided their informed signed consent, work-associated respiratory tract and voice symptoms (hoarseness or loss of voice, runny or stuffy nose, coughing, and dyspnoea) were recorded using a structured interview. If the patient was not sure whether a single symptom was more frequent at work, it was not considered to be work-associated.

4.2.2 Non-participating patients (Study II)

The patients that did not to take part in the study were examined in the departments of Occupational Medicine or Phoniatrics or Allergy Centre as indicated by their symptoms. To control for possible bias related to willingness to participate, based on patient records, their age, sex, line of business, main symptoms, and possible asthma diagnosis were evaluated.

4.2.3 Healthy controls (Study III)

For comparisons regarding laboratory and allergy test findings, subjects without any respiratory tract or voice symptoms were recruited as controls with similar proportions of women and men and different age groups as in the study population. They were recruited by the study group through personal networks and the aim was that they be of the same occupational fields as the study patients. Except for the absence of the CRP measurement, the healthy controls were subject to the same laboratory and allergy tests as the study patients. They also filled out the questionnaire including QEESI (chapter 4.7) and a question of work-related stress (chapter 4.8).

4.2.4 Population controls (Study IV)

For comparisons regarding QEESI questionnaire results, Finnish speaking people in the same hospital district were randomly selected by the Finnish Population Information System with similar proportions of women and men and different age groups as in the study population. The aim was to obtain 400 questionnaire answers (ratio 1:4) to increase the statistical power. Considering the recent rather low survey response rates, the questionnaire was sent to 1500 subjects.

4.3 Clinical examinations

The clinical tests conducted for the patients are presented in Table 2.

Table 2. The clinical tests conducted for the patients.

Lung function tests	2-week serial PEF monitoring, PEF monitoring at and off work, spirometry with bronchodilation test, methacholine challenge test, exhaled nitric oxide (FeNO), diffusing capacity of the lungs
Laboratory tests	Erythrocyte sedimentation rate, C-reactive protein (only to study patients), blood count, serum total IgE, serum allergen specific IgE (different fungi and storage mites *Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae*)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, *Dermatophagoides Pteronyssinus* house dust mite, latex, A*spergillus fumigatus*, storage mites *Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae*
Imaging	Chest x-ray, cone beam computed tomography of the paranasal sinuses

The diagnostic PEF monitoring included PEF measurements for two weeks in the morning and evening before and after an inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed according to European Respiratory Society/American Thoracic Society guidelines (Miller et al., 2005) and methacholine challenge tests were performed using a dosimeter with controlled tidal breathing according to the Finnish guidelines (Nieminen et al., 1988). Fractional exhaled nitric oxide concentration (FeNO) was measured during a single exhalation with a flow rate of 50 ml/s using a chemiluminescence analyzer (CLD 88, EcoMedics,

Switzerland) according to the international guideline (Horváth et al., 2017). The diffusing capacity was determined using the single breath method, so that the patient inhales a gas mixture containing methane and carbon monoxide to more than 85% of his vital capacity and holds breath for about 10 seconds. The diffusion capacity (DLCO) and lung alveolar volume (VA) and specific diffusion capacity (DLCO/VA) are then calculated from the dilution of methane and the reduction in the amount of carbon monoxide (Vyaire Medical, IL 60045, USA) (Hegewald, 2009).

IgE antibodies to different fungi that can be found in moisture damaged building structures (*Aspergillus fumigatus, Aspergillus versicolor, Acremonium kiliense, Cladosporium cladosporoides, Fusarium moniliformae, Penicillium species, Stachybotrys atra,* and *Trichoderma viridae*) were analysed using the ImmunoCAP system (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden) and fluoroenzyme immunoassay (FEIA). Specific IgE ≥ 0.35 kU/L was considered positive.

Since smoking can cause elevated leucocyte levels (Chabot-Richards and George, 2014) and decrease FeNO (Ahovuo-Saloranta et al., 2019), total leucocyte count (TLC) was analysed separately in nonsmokers and FeNO was omitted from smokers' testing.

Skin prick testing (SPT) was conducted using common allergen extracts (Soluprick, ALK A/S, Copenhagen, Denmark). These tests were performed by trained nurses according to a standardized protocol. The SPT was considered positive and showing sensitization to the allergen if the wheal size was at least 3 mm larger than the negative control.

Specialists in respiratory medicine, oto-rhino-laryngology (ORL) and phoniatrics examined the patients. An experienced phoniatrician assessed the participants' laryngeal status by indirect video laryngostroboscopy with a 90° rigid telescope (Olympus, Hamburg, Germany), a flexible fiberscope (ENF Type GP, SD video, Olympus, Hamburg, Germany) or a flexible naso-pharyngo videoscope (chip in tip, HD video, Olympus, Hamburg, Germany) with a straight and strobe light. Sprayed local anaesthesia (xylocaine spray) was used to prevent the gag reflex. To analyse the video recordings, the rpSzene® system (Rehder/Partner GmbH, Hamburg, Germany) was used.

4.4 Diagnostic criteria and definitions

4.4.1 Asthma

According to the Finnish asthma guidelines (Haahtela et al., 2013), the diagnosis of asthma must be confirmed with a demonstration of variable airway obstruction in lung function measurements (Table 3).

Table 3. The criteria for asthma diagnosis in different clinical tests (one positive finding required for asthma diagnosis) (Haahtela et al., 2013).

Clinical test	Criteria for asthma
Two-week peak expiratory flow (PEF) monitoring	At least 3 times - at least 15% and 60 L/min improvements of PEF after bronchodilator, or - diurnal variation of PEF at least 20% and 60 L/min
Spirometry	At least 200 mL and 12% improvement in forced expiratory volume in one second (FEV1) or forced vital capacity (FVC)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV1 (PD_{20}FEV1 <600 μg)

4.4.2 Occupational asthma

Concerning suspicion of occupational asthma caused by MD exposure, asthma diagnostics according to national guidelines (Haahtela et al., 2013), X-rays of the thorax and paranasal sinuses and basic laboratory tests (ESR, CRP, blood count and blood eosinophils) are needed. Building structural and indoor air investigations showing abnormal microbial growth compatible with MD in material samples in the vicinity of the employee's workplace and air connection from damaged material must

be available. In serial PEF monitoring at and off work, significant differences in measurements at the workplace and away from work must be seen. In these cases, the final occupational asthma diagnosis requires differential diagnostics in secondary health care (Lindström et al., 2009).

The four-week (serial) PEF monitoring at and off work was considered successfully performed, if it lasted at least for two and a half weeks, it included at least two work periods (at least three days each) and at least two periods away from work (at least two days each), the measurements were reliably performed at least four times per day, the measurements at and off work were equally frequent, and the monitoring was performed in the workplace with MD. There are no unambiguous criteria for when serial PEF monitoring refers to occupational asthma (Anees et al., 2004), but it requires expert evaluation based on measurement documentation and graphs (Lindström et al., 2011).

4.4.3 Upper airway disorders

The diagnostic criteria for chronic rhinosinusitis (CRS) were in accordance with the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 guideline (Fokkens et al., 2012), with symptoms of nasal discharge, nasal blockage, hyposmia, facial pressure/pain or nocturnal coughing for at least 12 weeks and signs of pus in the middle meatus, or pathologic imaging findings on CBCT scans.

To diagnose laryngeal dysfunctions, such as muscle tensions in the larynx in phonation, signs of glottic or supraglottic constriction during breathing at rest, hyperpnoea, or VCD, and organic laryngeal diseases, such as such as laryngitis, vocal fold polyp, node or other mucosal change, vocal fold atrophy, paresis or suspected paresis of recurrent or laryngeal superior nerve, international guidelines (Belafsky et al. 2002; Christensen et al., 2015; Morris and Christopher, 2010) were followed.

4.4.4 Atopy

Atopy was defined as at least one positive skin prick test reaction in the standard panel (birch, timothy, mugwort, horse, dog, cat, house dust mite *Dermatophagoides pteronyssinus*, and latex).

4.5 Assessment of multiple chemical sensitivity

The study patients, the healthy controls, and the population controls completed a questionnaire including the QEESI questionnaire which has been developed for use in research, as well as the clinical evaluation of patients reporting intolerances (Miller and Prihoda, 1999). Three QEESI subscales were used to assess possible MCS: the chemical intolerance subscale to determine which chemicals or odours possibly cause symptoms; the symptom severity subscale to examine the type and severity of the symptoms a person commonly experiences; and the life impact subscale to assess how the sensitivities affect different aspects of everyday life (Table 4).

Table 4. QEESI questionnaire subscales used to assess possible MCS and the assessed items within each subscale (Miller and Prihoda, 1999).

Chemical intolerance subscale	Symptom severity subscale	Life impact subscale
Engine exhaust	Muscle or joint problems	Diet
Tobacco smoke	Eye or respiratory tract problems	Ability to go to work or school
Insecticides	Heart or chest problems	Furnishing home
Gasoline	Stomach or digestive system problems	Choice of clothing
Paint or paint thinner	Problems with ability to think	Ability to travel or drive a car
Cleaning products	Mood problems	Choice of personal care products
Perfumes or fragrances	Balance or coordination problems	Social activities
Fresh asphalt or tar	Headache or feeling of pressure in the head	Choice of hobbies and recreation
Nail polish, nail polish remover or hairspray	Skin problems	Relationship with spouse and family
New furnishings	Urinary tract or genital problems	Ability to clean home and perform other routine chores

The respondents rated each item on different subscales between 0 and 10 points, with 0 meaning not at all a problem and 10 meaning a severe or disabling problem. The points of each subscale were tallied to obtain a total score from 0 to 100. On the chemical intolerance and symptom severity subscales, scores of 0-19 were classified as low, 20-39 as medium and 40-100 as high. On the life impact subscale, the respective scores were 0-11, 12-23 and 24-100. A high score class on the chemical intolerance subscale was used as a criterion for MCS. Based on previous research, this threshold has sensitivity of 83% and specificity of 84% for MCS (Miller and Prihoda, 1999).

The questionnaire was sent to the population controls by mail, and an opportunity to answer the questionnaire alternatively online was provided.

4.6 Assessment of work-related stress

Among the patients and healthy controls, work-related stress was assessed with a validated single-item question "Stress means a situation in which a person feels tense, restless, nervous, or anxious or is unable to sleep at night because his/her mind is troubled all the time. Do you feel this kind of stress these days?" by using a 5-point Likert scale from 0 "not at all" to 4 "very much". The responses were dichotomized into a low-stress level (responses from 0 to 2) or a high-stress level (3 and 4) (Elo et al., 2003).

4.7 Statistical analyses

To compare continuous variables, the independent samples t test and the Mann-Whitney test were used. The distributions of the parameters were analysed from descriptives (differences between mean and 5% trimmed means, skewness), Q-Q plots, and histograms. For categorical variables, the chi-squared test was used. Full blood count, ESR, CRP, total serum IgE, FeNO and skin prick testing were also analysed in relation to multiple chemical sensitivity (MCS) and perceived stress.

Data management and analysis were performed using IBM® SPSS® Statistics software, versions 25 (2017) and 28 (2021).

4.8 Ethical aspects

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Pirkanmaa Hospital District (protocol code R14095 and date 7 October 2014). Informed consent was obtained from all of the patients and symptomless controls involved in the study.

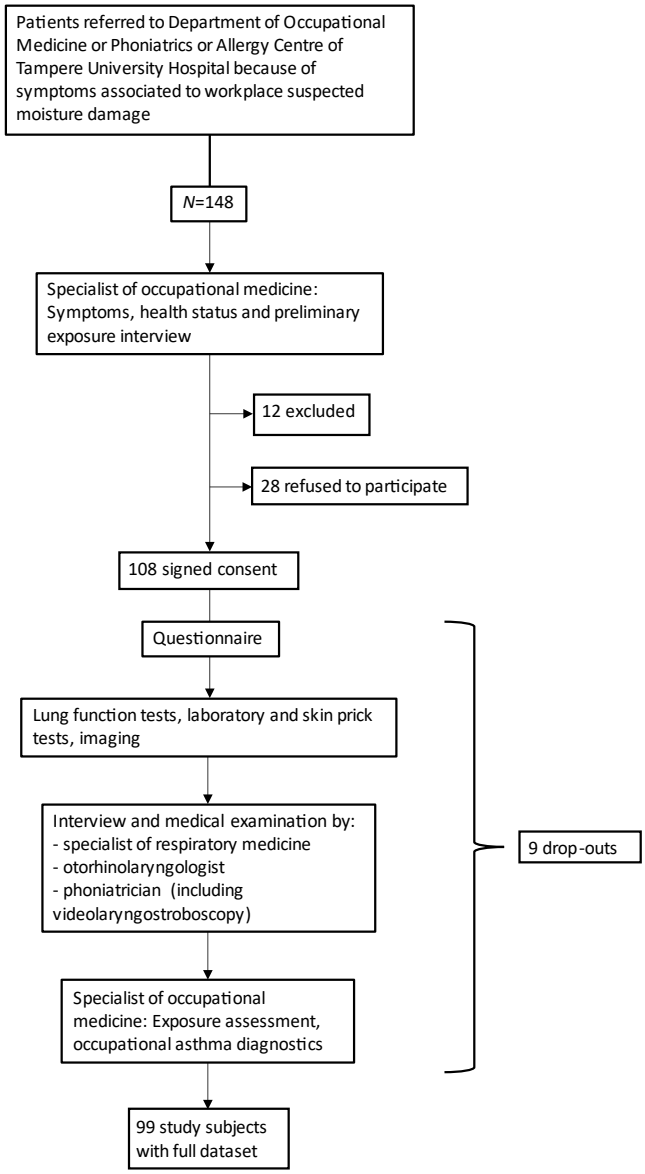
5 RESULTS

5.1 Characteristics of the study populations

5.1.1 Patients (Studies II-IV)

To reach a sample size of 100 patients, 148 patients were interviewed as possible study patients between October 2015 and June 2017. Twelve patients were excluded because they did not fulfil the inclusion criteria or fulfilled an exclusion criterion, 28 did not participate, and 108 provided their consent and participated. Eight patients did not want to proceed with clinical assessment and withdrew their consent before any visits and one after completing all the tests. The final study population consisted of 99 patients (Figure 2).

Figure 2. Selection of the patients and the course of the examinations.



Most of the patients (72%) were referred to secondary health care by their occupational health physicians. Table 5 shows the study patients' lines of business

grouped by standard industrial classification (Statistics Finland, 2008). The education personnel included 23 teachers, and the remainder were other school and academy workers. The patients from health services were nurses, practical nurses, and assistants. The study patients were not significantly exposed at work to other substances that could cause respiratory tract symptoms other than MD.

Table 5. The study patients' lines of business grouped by standard industrial classification.

Line of business	Study patients %
Education	29
Health services	26
Social services	12
Civil service and national defence	11
Industry or trade	11
Other	10

5.1.2 Non-participating patients (Study II)

Of the twenty-eight patients who did not want to participate or were unable to participate for practical reasons in the study, 86% reported hoarseness. Of the non-participating patients, 31% received a new asthma diagnosis when they were examined. The non-participating patients did not differ statistically significantly from the patients in terms of age, sex, line of business, or symptoms at the workplace (data not shown).

5.1.3 Healthy controls (Study III)

The healthy controls did not differ statistically significantly from the patients in terms of age, sex, and smoking (data not shown).

5.1.4 Population controls (Study IV)

The questionnaire was sent by post to the population controls in September 2017, and resent if the response had not arrived in five weeks. In the first round, 337 responses were received and the rest 225 were received after the reposting. Of the respondents, six persons filled out the questionnaire online. Altogether 568 (38%) of the population controls responded. Age, sex, and the proportions of women and men in different age groups did not statistically differ between the patients and the population controls (data not shown).

5.1.5 Background factors of the study populations

Mean age, gender, and smoking status of the study populations are presented in table 6.

Table 6. Age, gender, and smoking status of the study populations.

		Patients (n=99)	Non-participating patients (n=28)	Healthy controls (n=48)	Population controls (n=568)
Age	Range	20-63	22-62	21-60	21–63
	Mean	44	41	44	46
Female		82%	89%	77%	87%
Current smokers		9%	3%	4%	12%

5.2 Symptoms of the patients (Study II)

Based on referral information and interview, 99% of the patients reported hoarseness or loss of voice, 85% reported a runny or stuffy nose, 92% reported coughing, and 86% reported dyspnoea at the workplace. Five patients reported only upper airway symptoms without coughing or dyspnoea.

5.3 Asthma and other lower respiratory tract findings (Study II)

New-onset asthma was diagnosed in 30 patients, and two patients had had asthma before employment in the workplace with MD. Of the 30 new asthma diagnoses, 15 were confirmed by PEF monitoring, nine by findings on both PEF monitoring and spirometry or methacholine challenge testing, and six patients were diagnosed as having asthma based on spirometry or methacholine test results only.

The mean FeNO was 21.5 (2.6–63.0) ppb and the mean B-Eos was 206 (20–860) cells/μL in the 30 patients with new-onset asthma, while they were 20.6 (3.3–109.2) ppb and 169 (20–1010) cells/μL, respectively, in the patients without asthma. Among the new asthma cases, FeNO was >50 ppb in two (7%) patients and B-Eos was >300 cells/μL in five (17%) patients. Seven (23%) new-onset asthma patients had either elevated FeNO or elevated B-Eos.

Two patients with a smoking history of at least 15 pack-years had mild airway obstruction, and one of them fulfilled the diagnostic criteria for chronic obstructive pulmonary disease (COPD) (post bronchodilation $FEV_1/FVC < 0.7$).

The patients' chest X-rays yielded no clinically significant findings, and their pulmonary diffusing capacities of carbon monoxide were normal (mean 98% of predicted, range 73–131%). Ten patients were referred for further diagnostic testing by pulmonary specialists (one for HRCT and bronchoscopy, two for polysomnography, four for exercise testing, one for oesophageal pH and impedance recording, and three for additional blood tests). Based on these tests, two patients were diagnosed with hyperventilation syndrome (one of them also had asthma) and one asthma patient was diagnosed with moderate sleep apnoea.

5.4 Assessment of occupational asthma (previously unpublished)

Of the 30 new asthma (related temporally to workplace MD exposure) cases, 22 performed serial PEF (at and off work) monitoring acceptably. Of them, 10 had PEF decline at workplace. Three of the patients with new-onset asthma and serial PEF monitoring findings were referred to the Finnish Institute of Occupational Health expert group which did not find sufficient evidence of significant individual MD exposure at the workplace, overriding the diagnosis of occupational asthma according to the definition in the Finnish MD asthma agreement (Lindström et al., 2009). Concerning the remaining seven patients of the cases with PEF decline at

workplace, investigations in the workplace were not available or were so limited that individual MD exposure of these patients could not be estimated. None of the new-onset asthma cases were thus diagnosed as occupational asthma due to workplace MD.

There were seven non-asthma cases with serial PEF monitoring showing PEF decline at workplace. Of them, two had laryngeal changes or dysfunction, two had MCS, and two had both laryngeal findings and MCS.

5.5 Upper respiratory tract findings (Study II)

5.5.1 Clinical findings by the oto-rhino-laryngologist

Of the 98 patients who underwent the ORL examination, nasal endoscopy revealed that 36 (37%) patients had abnormal findings: 16 (16%) had nasal septal deviation, 9 (9%) had irritated or crusty nasal mucosae, 6 (6%) had watery clear discharge, 1 had a nasal septal perforation, and 1 had signs of an acute viral infection. CBCT of the paranasal sinuses was conducted on all the study patients. The criteria for CRS, including the symptoms and findings from the CBCT images, were met by 11 (11%) patients. The CBCT images showed that 34 (34%) patients had anatomical abnormalities such as concha bullosa or hypoplastic paranasal sinuses, 28 (28%) had swollen mucosa in their nasal cavities or in the paranasal sinuses, 7 (7%) had high dental roots, 5 (5%) had signs of previous endoscopic sinus surgery, and 8 (8%) had fluid retention in their sinuses.

5.5.2 Clinical findings by the phoniatrician

Organic laryngeal findings were observed in 21 (22%) of the 96 participants who underwent the phoniatrician's clinical examination. The organic findings were either mucosal (such as laryngitis, vocal fold polyps, node or other mucosal changes, and vocal fold atrophy) or neurological (paresis or suspected paresis of recurrent or laryngeal superior nerve). Signs of laryngeal dysfunction were observed in 27 (28%) participants: muscle tensions in the larynx in phonation (primary muscle tension patterns), signs of glottic or supraglottic constriction during breathing at rest or hyperpnoea. Vocal cord dysfunction (VCD) was found in three (3%) patients.

Organic or functional laryngeal findings were found in 12 (39%) patients with asthma and 30 (46%) patients without asthma (p=0.492).

5.6 Inflammatory markers (Studies II-IV)

5.6.1 IgE mediated sensitization

At least one positive SPT reaction in the standard panel (birch, timothy, mugwort, horse, dog, cat, *Dermatophagoides Pteronyssinus* house dust mite, latex) was found in 37%, and sensitization to any pollen was found in 34% of the study patients. Comparison of the study patients with asthma (n = 32) and without asthma (n = 67) revealed no significant differences in the rates of sensitization to any of the tested standard panel allergens (46% vs. 33%, p = 0.275) or *Aspergillus fumigatus* (3% vs. 1.5%, p = 1.000). The patients' allergen specific IgE showed no sensitization to the different fungi investigated.

None of the patients had IgE antibodies to the storage mites *Acarus siro* and *Lepidoglyphus destructor*, but one patient had specific IgE antibodies to *Thyrophagus putrescentiae* (0.46 kU/L). Of the symptomless controls, one was sensitized to all of the storage mites tested: specific IgE to *Acarus siro* was 1.8 kU/L (SPT 5 mm, negative control 0), to *Lepidoglyphus destructor* was 1.63 kU/L (SPT 4 mm) and to *Thyrophagus putrescentiae* was 2.31 kU/L (SPT 5 mm). In addition, one control's *Thyrophagus putrescentiae* specific IgE was 0.64 kU/L without a positive SPT reaction, and one had positive IgEs to all three storage mites (0.77-0.82 kU/l) with positive SPT reaction only to *Acarus siro* (5 mm, negative control 2 mm) (previously unpublished).

5.6.2 Other laboratory test findings

The total leucocyte count was elevated (>8.2 x109/L) in 17% of the patients and in 4% of the symptomless controls (p=0.050). In the nonsmokers, the respective proportions were 17% and 2% (p=0.019). Among the patients, elevated total leucocyte counts were found in 28% with and 12% without asthma (p=0.108), and in 18% with and 17% without CRS (p=1.000). The neutrophil count was elevated (>6.20 x109/L) in 8.1% of the patients and in none of the controls (p=0.055). Among the patients, elevated neutrophil counts were found in 19% with and 2%

without asthma (p=0.003), and in 9% with and 7% without CRS (p=0.714). Lymphocyte counts were elevated (>3.50 x109/L) in 4.1% of the patients and in none of the controls (p=0.329). There were no other significant differences in blood counts (red blood cell indices, thrombocyte count, basophils, and monocytes) between the patients and the controls.

FeNO (only nonsmokers included in the analysis) was 2.6-109 ppb among the patients (median 17.0 ppb) and 5.7-60.5 ppb among the controls (median 17.1 ppb, p=0.507). The ESR was 2-40 mm/h among the patients (median 6 mm/h) and 2-22 mm/h among the controls (median 5 mm/h, p=0.043). Total IgE was 0-715 kU/L among the patients (median 30 kU/L) and 1-671 kU/L among the controls (median 30 kU/L, p=0.725). CRP among the patients ranged from <1.0 to 29 mg/L (median 1.20 mg/L).

5.7 Work-related stress (Study III)

The level of stress was high among 26% of patients and 6% of controls (p=0.005). The level of perceived stress was related only to an increased count of blood monocytes in the study patients (p=0.016), and not to CRP, FeNO, ESR, or total IgE level.

5.8 Multiple chemical sensitivity (Study IV)

5.8.1 Multiple chemical sensitivity among patients

Among the study patients, 39% had high scores in the chemical intolerance subscale, 60% in the symptom severity subscale, and 53% in the life impact subscale. The gender difference did not reach statistical significance among the study patients in chemical intolerance (43% and 24%, respectively, p = 0.114) or symptom severity subscales (60% and 59%, respectively, p = 0.575), but women had high scores more often in the life impact subscale (57% and 29%, respectively, p = 0.033).

No statistically significant differences were found in the comparisons of subscale results between patients with and without asthma, with/without asthma and/or CRS, with/without laryngeal dysfunction or organic change, or with/without atopy (Table 7).

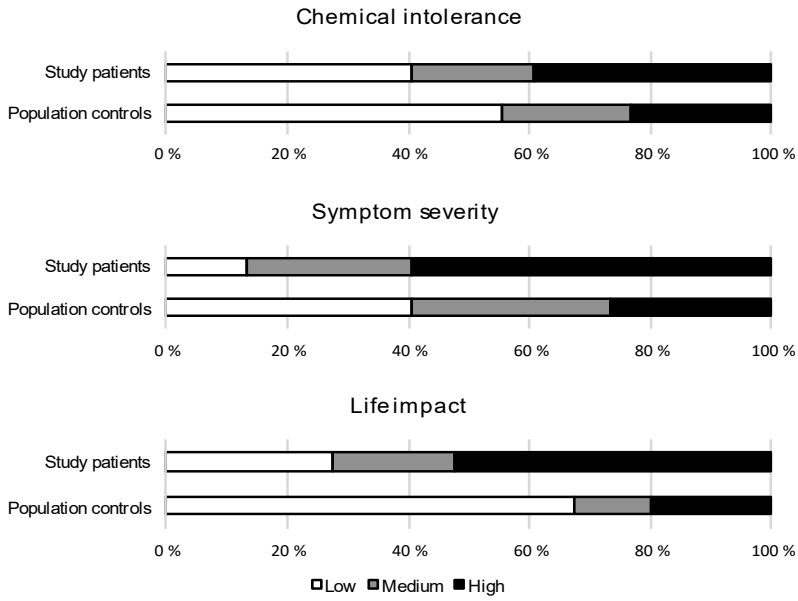
Table 7. Proportions of study patients with different illnesses or findings reporting high scores in the chemical intolerance, symptom severity, and life impact subscales (CRS: chronic rhinosinusitis).

	Asthma (n=32)			Asthma and/or CRS (n=39)			Laryngeal problem (n=42)			Atopy (n=37)		
Subscale	yes %	no %	p	yes %	no %	p	yes %	no %	p	yes %	no %	p
Chemical intolerance	44	37	0.661	42	36	0.675	48	33	0.207	30	45	0.143
Symptom severity	63	58	0.827	59	60	1.000	60	59	1.000	60	60	1.000
Life impact	50	54	0.830	46	57	0.410	56	52	0.837	51	53	1.000

5.8.2 Comparison of multiple chemical sensitivity between study patients and population controls

The patients had significantly more often high scores in the chemical intolerance (39% vs. 23%, $p = 0.001$), the symptom severity (60% vs. 27%, $p < 0.001$), and the life impact (53% vs. 20%, $p < 0.001$) subscales than the controls (Figure 3). The proportion of subjects scoring high on all the three scales was 26% among the patients and 9% among the controls ($p < 0.001$).

Figure 3. Proportions of subjects with low, medium, and high scores in chemical intolerance (p = 0.002), symptom severity (p < 0.001), and life impact (p < 0.001) among patients and controls (X^2 testing with 3 × 2 cross-tabulation).



5.8.3 Comparison of multiple chemical sensitivity between women and men among population controls

Among the population controls, women had more often high scores in each of the three subscales compared to men: 25% vs. 10% (p = 0.001) in chemical intolerance, 29% vs. 10% (p < 0.001) in symptom severity, and 22% vs. 5% (p < 0.001) in life impact.

5.8.4 Multiple chemical sensitivity and laboratory test results

MCS was not significantly associated with any laboratory test result (data not shown).

6 DISCUSSION

6.1 Major findings of the study

6.1.1 Asthma and other lung disorders

This clinical observational study consisted of 99 patients referred to secondary health care due to workplace moisture damage associated respiratory tract or voice symptoms. The mean age of the patients was 44 years (20-63) and 83% of them were female. In our study population, of the individuals with respiratory tract symptoms such as coughing and dyspnoea, approximately one-third had lower airway dysfunction compatible with asthma. Additionally, most of the patients with symptoms that could be interpreted as asthma showed no evidence of variable or reversible airway obstruction (Aaron, 2017; Gershon, 2012).

Interestingly, only 7 of the 30 new-onset asthma cases had signs of type 2 inflammation (2 had increased FeNO and 5 had increased levels of blood eosinophils). The proportion of type 2 asthma in our study population was much lower than usually seen in adult-onset asthma (Ilmarinen et al., 2017; Wenzel, 2012). Additionally, among patients with asthma, elevated neutrophil counts were more common than among patients without asthma. This finding does not necessarily indicate that a large number of asthma cases in these patients is associated with airway neutrophilic inflammation, since it can only be reliably assessed from airway samples (Porsbjerg et al., 2018). MD could also be associated with asthma caused by chronic low-level irritation, which in turn is linked to non-eosinophilic endotypes of asthma (Vandenplas et al., 2014). This finding is in line with a study of nasal biopsy gene expression and plasma cytokine profiles that found less airway and systemic inflammation in MD-associated asthma than in asthma not associated with MD exposure (Suojalehto et al., 2021).

None of the patients showed signs of hypersensitivity pneumonitis (HP; extrinsic allergic alveolitis), which some papers have associated with indoor MD exposure (Eerikäinen et al., 2013; Selman et al., 2012).

In our study, allergic sensitization was as common among the patients as among the symptomless controls, and equally common among the patients with and without asthma. The prevalence of sensitization among our patient group was in line with earlier findings in general population (Pallasaho et al., 2006). This finding agrees with a review by Mendell et al. (Mendell et al., 2011) which found MD exposure-associated health effects in both allergic and nonallergic persons. Based on previous research, CRS, allergic rhinitis and asthma are significantly interrelated in the general population (Rosati and Peters, 2016). However, within our study population, no such interrelation was found. Considered together, allergic mechanisms did not seem to explain the symptoms related to workplace MD exposure.

Overall, since allergic sensitization was equally common among the patients and symptomless controls, routine testing for possible sensitization among these patients is not useful considering that the symptoms are workplace related.

6.1.2 Occupational asthma

There are no international uniform criteria for occupational asthma diagnosis related to MD at workplace. According to the Finnish agreement, the occupational asthma diagnosis due to MD exposure at workplace requires asthma diagnosis with sufficient differential diagnostics, PEF decline in workplace in serial PEF monitoring, and evidence of significant MD exposure at workplace (Lindström et al., 2009). In this study, of the 30 new-onset asthma cases, none were diagnosed with occupational asthma. The problematic points in occupational asthma diagnostics based on this study are the performance of serial PEF monitoring at and off work and establishing significant MD exposure in the workplace. Serial PEF monitoring was not always conducted in occupational health care prior to referring to secondary health care, or its quality was not acceptable due to e.g., large number of missing values. Also, a part of the patients had already moved to another workplace. MD exposure assessment is always based on documents received from employer. From the employer's or building owner's point of view, the purpose of the investigations is to find out and locate the source of indoor air problem in the building, and to plan necessary remediation measures. Thus, the investigations are possibly not carried out in the vicinity of the symptomatic employee, and they provide little information for the assessment of individual exposure to MD related microbes.

Interestingly, seven non-asthma cases had PEF decline at the workplace in serial PEF monitoring. This outcome is in line with the study of White et al. in which two

of the five subjects with work-related patterns did not have asthma (White et al., 2013). Of the non-asthma patients, six had laryngeal changes and/or MCS referring to functional mechanisms underlying the PEF changes in serial monitoring. In previous research, glottis surgery has been shown to influence spirometry results including PEF (Leitersdorfer et al., 2005) indicating that PEF results might also reflect airflow in the upper airways.

6.1.3 Laryngeal findings

Organic laryngeal changes were more common (22%) in this study than in a previous study of 78 healthy Finnish female teachers, which found organic laryngeal changes in 14% of the cases (Ilomäki et al., 2009). However, no previous research is available on how common functional laryngeal findings are among individuals with or without symptoms. Organic or functional laryngeal findings were equally common in patients with and without asthma. A recent meta-analysis estimated that the prevalence of laryngeal dysfunction among adult asthmatics is 25% (Lee et al., 2020) but how common organic laryngeal findings are among asthma patients is not known.

Respiratory tract symptoms could also be explained by an irritable larynx, a term referring to a hyperreactive larynx causing increased muscle tension in the laryngeal muscles, dyspnoea due to laryngeal constriction, coughing, and voice problems (Morrison et al., 1999). Our study did not enable us to draw conclusions regarding whether MD exposure could cause irritable larynx or whether irritable larynx is the primary reason for symptoms in a workplace with MD. Either way, in the case of laryngeal disorders, asthma medication does not help or might even worsen symptoms if the larynx is sensitive to irritation (Idrees and FitzGerald, 2015). Coexisting with asthma, symptoms of laryngeal origin could be misinterpreted as an insufficient response to asthma treatment. Thorough differential diagnostics and the correct use of asthma medication are thus recommended to avoid unnecessary prolonged symptoms.

Hoarseness or loss of voice at workplace was reported by 99% of the patients, but at the first study visit its severity was not evaluated. According to previous studies, voice disorders are found much less frequently in the general population, reported by 17–39% (Lyberg-Åhlander et al., 2019; Spantideas et al., 2015). The prevalence of voice disorders among teachers and day care centre teachers is high (Laukkanen et al., 2008; Trinite, 2017), but in this study most of the patients were from occupations that are not especially demanding concerning the use of the voice.

Hoarseness among the patients without laryngeal findings could be associated with factors other than voice strain, such as the actual irritative effect of MD exposure or psychological factors (de Brito Mota et al., 2019).

6.1.4 Nasal findings

Most of the patients (85%) reported having a runny or obstructed nose in the workplace, but clinical findings in the ORL examination were rather infrequent. None of the patients had acute bacterial rhinosinusitis. Overall, the clinical findings in the upper respiratory tract seemed to be rather modest in the study population, suggesting that most MD exposure-associated nasal symptoms could be attributed to irritation by indoor air impurities. Together with nasal congestion, a sensation of paranasal sinus pressure is often reported by MD-exposed patients (Cummings et al., 2013). Tools are needed to differentiate congestion symptoms from acute or chronic rhinosinusitis among these patients.

6.1.5 Inflammatory markers

Among the patients, slight elevations in blood leucocyte and neutrophil counts were found. These findings were not associated with diagnosed CRS. Serum total IgE levels did not differ between patients and controls, in line with previous studies among subjects with workplace MD exposure (Purokivi et al., 2001; Zhang et al., 2012).

The levels of CRP and ESR were low, indicating a low probability of inflammatory processes or infections explaining the symptoms (Sproston and Ashworth, 2018). The level of CRP has previously been shown to be associated with MD in main living areas at home among children (Mustonen et al., 2016). This discrepancy could be attributed to different immunological responses in children, but CRP remaining low among the patients in this study could suggest that the quality of MD exposure at the workplace is unable to induce systemic inflammatory responses. Additionally, that FeNO and B-eos levels remained normal in most of the patients, in contrast to previous studies among employees from workplaces with MD (Norbäck et al., 2016; Zhang et al., 2012), could indicate different exposures among the patients.

The level of perceived stress in the study patients was related to an increased monocyte count. This result is in line with a previous study (Heidt et al., 2014) but

likely has little clinical importance. The finding of neutrophilia associated with stress in the study by Heidt et al. was not confirmed in this study. In contrast to some previous studies (Johnson et al., 2013; Xu et al. 2015), CRP was not associated with perceived stress in this patient group.

6.1.6 Multiple chemical sensitivity

MCS was significantly more prevalent among the patients with workplace MD-associated respiratory tract or voice symptoms than among the general population. The most prominent differences between study patients and the general population were in experiencing symptoms and in the effects of sensitivities on different aspects of everyday life. The prevalence of MCS in the general population was higher in this study (23%) than in the questionnaire study by Karvala et al. (15%) (Karvala et al., 2018). However, that study was conducted in a certain geographical area of Finland, Ostrobothnia in Western Finland, and the prevalence of self-reported chemical intolerance was assessed with one question. More in line with our study is the study of Vuokko et al. of fertile-aged women in Eastern Finland, in which chemical intolerance was determined if the respondent reported intolerance to at least two of the six chemical items considered. Of the respondents, 29% reported annoyance from chemicals without any symptoms and 23% reported annoyance with one or more symptoms (Vuokko et al., 2018). The prevalence of MCS also varies depending on the target population and on the method and criteria used. Studies using the QEESI on the general population in other countries have resulted in the prevalence of 8–22% depending on the use of different subscale combinations (Heo et al., 2017; Hojo et al., 2009; Skovbjerg et al., 2012).

Among the population controls in this study, women had more often MCS than men. This is in line with previous studies (Heo et al., 2017; Skovbjerg et al., 2015). There was no significant difference between the proportions on women and men in patients and population controls. Thus, the predominance of women in patients did not explain that the patients had MCS more often than the population controls.

Rather than only determining whether a person has symptoms associated with different chemicals, it would be important to examine how severe the symptoms are and how much chemical intolerance affects the person's life. In the previously mentioned study of Vuokko et al., 9.9% of the respondents also reported behavioural changes to avoid symptoms and 5.7% reported disabilities, e.g., disability to work, related to their sensitivities (Vuokko et al., 2018). Respectively, a

combination of the three QEESI subscales (chemical intolerance, symptom severity, and life impact) could be a means of identifying the most disabling cases of MCS in practice. Receiving high scores in all three subscales indicates that a person has symptoms in association with several chemicals and in different organ systems, and the symptoms considerably affect the person's everyday life. In our study, the proportion of controls receiving high scores in all three subscales was 9%. Of the study patients, 26% received high scores in all three subscales indicating that a considerable proportion of their symptoms could be attributed to MCS. Whether patients were diagnosed with asthma, asthma and/or chronic rhinosinusitis, laryngeal problems, or allergic sensitization did not influence MCS findings. This finding is contradictory to previous questionnaire studies reporting MCS being more common among subjects with respiratory tract inflammatory diseases and atopy (Azuma et al., 2019; Claeson et al., 2018; Lind et al., 2017). MCS symptoms can, however, be misinterpreted as respiratory tract diseases or allergic symptoms in questionnaire studies.

6.2 Methodological aspects

This type of comprehensive clinical study, describing the findings in patients with symptoms associated with workplace MD exposure, has not been conducted before. Its strength is in its extensive systematic clinical testing and specialist evaluations of patients exposed to MD in the workplace, increasing understanding of symptoms and diagnoses and whether they relate to the symptoms experienced. While previous studies in this area have been mainly epidemiological, this study provides additional information specifically at the individual level.

Our study sample represented a population of subjects with respiratory tract or voice symptoms related to workplace MD exposure. We estimated that a sample of 100 patients would be sufficient for the clinical evaluation of patient characteristics. The main aim of this study was to describe the results and diseases found among individuals referred to secondary health care due to symptoms associated with workplace MD. Of all of the workers exposed to MD at the workplace, only those who have symptoms (either due to MD exposure or coexisting with MD exposure) contact (occupational) health services and can eventually be referred to secondary care. Thus, the patients in this study were a selected group of workers whose probability of having asthma was higher than that of the general population or even of workers exposed to MD. No similar previous studies exist for comparison, and

this type of study design precludes any conclusions regarding asthma incidence related to workplace MD exposure.

The strengths of this study are the systematic clinical examinations of workplace MD-exposed patients with the assessment of possible MCS using a questionnaire charting the chemicals that possibly cause symptoms, the type and severity of the symptoms that a person commonly experiences, and how the sensitivities affect different aspects of everyday life, and the comparison of MCS results to the general working-age population. As seen in previous studies, MCS prevalence can vary depending on the target population within the same country, which is why the controls were selected to be of working age and from the same region as the patients.

The study population consisted of patients referred to secondary health care by physicians who considered the patient's symptoms sufficiently difficult to warrant further diagnostics. Information on the study was not publicly announced, so awareness of it would not have influenced the decision to refer. The study population and population controls were recruited before the Finnish guidelines for examining patients with symptoms associated with MD were published (Patient exposed to moisture damage: Current Care Guideline Abstract, 2017). The non-participants did not differ significantly from the study patients, decreasing the likelihood of bias related to willingness to participate in the study. Based on these facts, it is justified to claim that the group of study patients is a good representation of employees referred for symptoms associated with MD in the workplace.

In Finland, which is located in the subarctic region, it is estimated that 20–26% of hospitals and health care centres and 12–18% of schools and kindergartens have significant MD, whereas in office buildings the respective proportion is estimated to be 2.5–5% (Borràs-Santos et al., 2013; Reijula et al., 2012). The large proportion of teaching and health service personnel among the study patients could at least partly explain the more frequent findings of MD at their workplaces. Approximately 80% of primary-level teachers in Finland are women (The World Bank Data; Primary Education Teachers, Finland, 2019). In the Finnish trade union for health care employees, 92% of the members are women (Tehy Statistics, 2019). The large proportion of women in our study is thus at least partly due to more women working in public buildings that have MD. However, there is also evidence that women report more symptoms than men related to indoor air problems at the workplace (Lee et al., 2018; Reijula and Sundman-Digert, 2004), which might also have contributed to the female predominance in our sample.

There are some limitations of the study. The response rate in the questionnaire for the controls in this study was quite low (38%), reflecting the current willingness

to participate in surveys in general. Even if the gender proportions in all and among the different age groups of the study patients and controls were satisfactorily alike, those who are generally interested in the subject and perhaps more concerned about the effects of environmental factors on their health are probably more likely to participate in the survey, possibly causing the prevalence of MCS in the general population to be overestimated. The setup to compare MCS findings in a selected group of patients and the regional population can be questioned since there is limited knowledge on the background factors, in addition to the age and gender of the controls. However, there is no information on, e.g., MCS in different occupations to favour inspection based on occupation. Furthermore, considering the present conception of the mechanism of MCS, knowledge about the possible MD exposure of the controls is not essential. In addition, there is no knowledge about MCS prevalence among different patient groups in secondary health care.

Some of the patients had already changed to another department within the same workplace or even resigned due to symptoms that they considered difficult. Additionally, for some patients, the examinations were delayed for up to six months due to lacking research resources. However, delays are common in outpatient clinics, and among these patients, delays in investigations likely did not significantly affect the results.

A common feature of descriptive studies is that they do not offer the possibility of finding causal connections between exposure and health outcome (Grimes and Schulz, 2002). However, associations can be found, yielding hypotheses for future research.

7 SUMMARY AND CONCLUSIONS

The aim of this thesis was to describe the patient characteristics, the prevalence of different symptoms, and the clinical findings in secondary healthcare, among patients with workplace MD- associated respiratory tract or voice symptoms. A special interest in this study was in improving the differential diagnostics among asthma, laryngeal findings, and multiple chemical sensitivity (MCS).

In patients referred to secondary health care dur to workplace MD- associated respiratory tract or voice symptoms, the main findings were:

1) New-onset asthma was diagnosed in 30 (30%) patients. Type 2 inflammation was clearly less common than that usually seen in adult-onset asthma, and together with elevated neutrophil count among patients with asthma, could indicate that moisture damage associated asthma is related to chronic low-level irritation.

2) Functional or organic changes in the larynx were frequent among patients both with and without asthma. Symptom based diagnosis of asthma without lung function testing could cause considerable over diagnosing of asthma in patients with symptoms related to MD, since many of them likely have laryngeal symptoms only and not true asthma.

3) MCS was common, and the symptoms considerably affected the patients' everyday lives. Asthma, chronic rhinosinusitis, laryngeal problems, and allergic sensitization were not associated with the presence of MCS.

4) Most of the patients (85%) reported having a runny or obstructed nose in the workplace, but only 11% had chronic rhinosinusitis, and none had acute bacterial rhinosinusitis. There were no basic laboratory or allergy test results characteristic of this patient group.

5) Among the patients, there were 30 new asthma cases that had developed in temporal connection with MD exposure. However, none of them were diagnosed as occupational asthma. The Finnish practice to diagnose MD associated occupational asthma seems to be challenging in that the necessary information to assess exposure at the workplace is not often available.

The findings of this study have some practical implications. To avoid unnecessary or symptom-worsening asthma medication, proper differential diagnostics with lung function testing and, evaluation of the larynx and its function are needed. MCS should be considered a possible explanatory factor for MD-associated symptoms. It seems reasonable that the possibility of MCS being one factor explaining the symptoms could be discussed at the beginning of the patient's examinations. Inflammatory processes should be excluded with basic laboratory tests, but the use of allergy tests does not seem necessary when the symptoms are clearly workplace associated.

Based on this study, future research is needed to clarify certain points. Laryngeal findings were common in this patient group, but this finding requires confirmation, e.g., by comparison to laryngeal findings in symptomless subjects. The proportion of type 2 asthma in our study population was much lower than that usually seen in adult-onset asthma. The assessment of whether workplace MD-associated asthma is different from asthma in general calls for follow-up research and studies with sputum samples or bronchial biopsies. Considering serial PEF monitoring at and off work in the diagnostics of occupational asthma, comparisons of findings among subjects with asthma and laryngeal symptoms without asthma with (remote) recording devices would be useful, first to exclude possible effects of incorrect blowing techniques and second to determine the frequency of PEF changes in laryngeal disorders. The ability to recognize patients with true rhinosinusitis among patients with upper respiratory tract symptoms is also needed. Factors affecting MCS relief or worsening would be useful to study in follow-up.

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PUBLICATIONS

PUBLICATION I

Observational cross-sectional study on Symptoms Associated to Moisture DAmage at Workplace: the SAMDAW study protocol

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BMJ Open. 2019 Jun 25;9(6):e026485. doi: 10.1136/bmjopen-2018-026485

BMJ Open

Observational cross-sectional study on Symptoms Associated to Moisture DAmage at Workplace: the SAMDAW study protocol

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To cite: Nynäs P, Vilpas S, Kankare E, *et al*. Observational cross-sectional study on Symptoms Associated to Moisture DAmage at Workplace: the SAMDAW study protocol. *BMJ Open* 2019;**9**:e026485. doi:10.1136/bmjopen-2018-026485

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-026485).

Received 4 September 2018
Revised 6 June 2019
Accepted 7 June 2019

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ABSTRACT

Introduction Moisture damage (MD) exposure at work has been shown to increase the risk of new onset asthma and exacerbation of asthma. However, most of the studies in this field have been questionnaire studies. A small proportion of MD-exposed workers are diagnosed with asthma. Many patients with MD exposure at work referred to secondary healthcare report intermittent hoarseness, loss of voice or difficulty to inhale, referring to functional or organic problems of the larynx. For accurate treatment, proper differential diagnostics is paramount. We present an ongoing observational study in which we describe the prevalence of respiratory, voice and other symptoms related to MD at work in patients referred to secondary healthcare. Case-control setting will be used to evaluate the frequencies of the background factors, bronchial hyperreactivity and laryngeal findings.

Methods and analysis The study sample consists of patients with workplace MD exposure and associated respiratory tract and/or voice symptoms referred to Tampere University Hospital. The clinical tests conducted to the study patients included comprehensive lung function tests, laboratory and skin prick tests, imaging and clinical evaluation by specialists of respiratory medicine, oto-rhino-laryngology and phoniatrics. The exposure assessment was performed by an occupational physician. The study patients filled out a questionnaire on previous illnesses and other background factors, which for comparison was also sent to 1500 Finnish-speaking people in the same hospital district randomly selected by the Finnish Population Information System. To explore how common laryngeal disorders and voice symptoms are in general, a part of the tests will be conducted to 50 asymptomatic volunteers.

Ethics and dissemination The regional ethics committee of Tampere University Hospital approved the study. All study subjects gave their written informed consent, which is required also from the controls. The results will be communicated locally and internationally as conference papers and journal articles.

Strengths and limitations of this study

- ► This kind of comprehensive clinical study associated with moisture damage exposure at work has not been conducted before.
- ► This study will increase the understanding of respiratory tract and voice symptoms and associated clinical findings in subjects exposed to moisture damage.
- ► Information on moisture damage exposure at work is based on documents from the workplace.
- ► Limitation of a cross-sectional study like this is that it is not possible to obtain information on causal relationships between exposure and symptoms or illnesses.

INTRODUCTION

Indoor air quality problems are considered important risk factors for health problems worldwide.[1] Indoor air-associated symptoms may be interrelated with different indoor air factors such as insufficient ventilation,[2] unfavourable temperature conditions,[3] dry indoor air,[4] dustiness,[5] moisture damage (MD),[1] volatile organic compounds (VOC),[6] and man-made mineral/vitreous fibres (MMMF/MMVF).[7] Even if we do not know the cause of symptoms,[1] MD exposure at work has been shown to increase the risk of new onset asthma and exacerbation of asthma.[8 9] Other illnesses or respiratory symptoms that have been associated with MD exposure include cough, wheezing, dyspnoea, rhinitis and upper respiratory tract symptoms.[9 10]

In Finland, located in subarctic area, MDs in residences and schools are common.[11] Workers in office buildings commonly report symptoms and complaints associated with indoor air.[12 13] There is also a growing public concern over MDs in buildings and their possible permanent effects on dwellers' or workers' health in Finland, even if there is minor evidence of serious or permanent illnesses other than asthma caused by exposure to MD.[9 14]

There are few studies describing the clinical findings in patients having symptoms when exposed to MD at work.[15 16] Previous studies in this field have mainly been epidemiological,[9] and most is known about children's risk of developing symptoms in homes or schools with MD.[17 18] In majority of the studies, the assessment of exposure to MD or presence of symptoms or illnesses has been based on questionnaires.[19 20] Furthermore, only a small proportion of MD-exposed workers are diagnosed with asthma.[8] According to our clinical experience, many patients with work-related MD exposure and referred to secondary healthcare report intermittent hoarseness, loss of voice or difficulty to inhale, which would refer to functional or organic problems of the larynx.[21] In the case of laryngeal disorders, asthma medication is not useful or may even worsen the symptoms if the larynx is sensitive to irritation.[22] Coexisting with asthma, laryngeal disorders may be the cause of insufficient response to asthma treatment.

Studies over the past decades have provided important information on idiopathic environmental intolerance (IEI), in which a person has symptoms from different organ systems when in contact with an environmental factor that does not cause symptoms to most people.[23 24] In odour or multiple chemical sensitivity (MCS), a person reacts with symptoms in association with low levels of airborne chemicals that most people tolerate without problems.[25 26] It seems that some proportion of the patients who have indoor air-associated symptoms in fact have IEI/MCS, but the frequency of this condition among these patients is not known.[27]

As a conclusion, there is a need for a clinical study on patients exposed to MD at workplace focusing especially on differential diagnostics between asthma and laryngeal symptoms, evidence of exposure to MDs and other indoor air risk factors and chemical sensitivity.

Aims of the study

In patients referred to secondary healthcare because of respiratory tract and/or voice symptoms associated to MD exposure at work, the aims are to

1. Describe the prevalence of different characteristics, symptoms and clinical test findings.
2. Find out the frequency of laryngeal symptoms and their possible influence on asthma diagnostics.
3. Explore the number of patients who fulfil the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory (QEESI)© question series.[28]
4. Find out if there are connections between abovementioned symptoms and clinical findings and if it would be possible to allocate the clinical tests according to patient's symptoms in secondary healthcare.

METHODS AND ANALYSIS

The study is conducted at Tampere University Hospital, which is a secondary level referral centre for a population of 530 000 and a tertiary level referral centre for a population of about 1 million people. Patients referred to departments of Occupational Medicine or Phoniatrics or Allergy Centre because of symptoms associated with indoor complaints at their workplace were interviewed as possible study subjects between October 2015 and June 2017. The study inclusion criteria were as follows: (1) age between 18 and 65 years, (2) upper and/or lower respiratory tract and/or voice symptoms, (3) symptoms associated to workplace and (4) at least a strong suspicion of MD at the workplace (box 1). The exclusion criteria were as follows: (1) severe illness (eg, cancer) and (2) pregnancy. The study design is presented in figure 1. After the study subjects had given their informed signed consent, the work-associated symptoms were collected by a structured interview. If the patient was not sure if the symptom

Box 1 The criteria on which moisture damage (MD) at workplace was suspected.[13]

1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant.
2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials, disengaging or blistering of flooring materials, crumbling of wall plastering, water leakages through ceilings (buckets on the floors), loose water on surfaces.
3. Renovations because of MDs previously made in the building.
4. Information on MD findings from employer or occupational and health safety personnel.

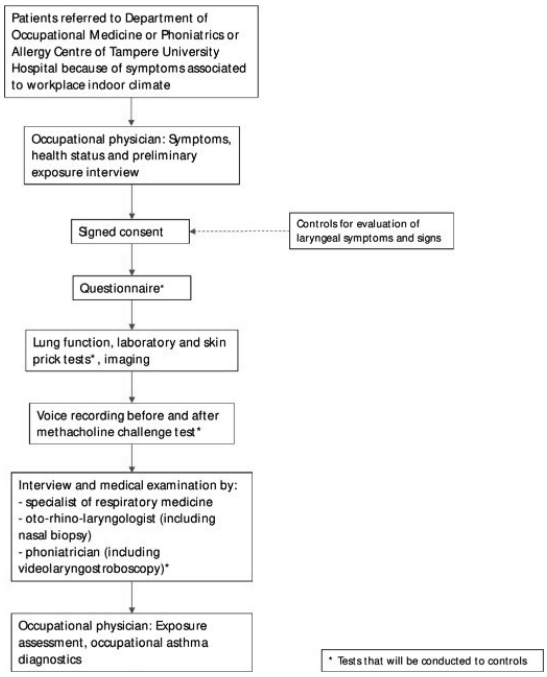

Figure 1 The study design on symptoms associated to moisture damage at workplace.

Table 1 The clinical tests conducted to the study patients

Lung function tests	Two-week serial PEF monitoring, PEF monitoring at and off work, spirometry with bronchodilation test, methacholine challenge test, exhaled nitric oxide (FE_{NO}), diffusing capacity of the lungs
Laboratory tests	Sedimentation rate, C-reactive protein, blood count, serum total IgE, serum allergen-specific IgE (different fungi and storage mites Acarus Siro, Lepidoglyphus Destructor, *Tyrophagus putrescentiae*)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, Dermatophagoides Pteronyssinus house dust mite, latex, aspergillus fumigatus, storage mites Acarus Siro, Lepidoglyphus Destructor, *Tyrophagus putrescentiae*
Imaging	Chest x-ray, cone beam CT of the paranasal sinuses

PEF, peak expiratory flow.

was more frequent at work, it was not considered to be work associated.

The conducted clinical tests are presented in table 1. According to Finnish asthma guideline,[29] diagnosis of asthma must be confirmed with a demonstration of variable airway obstruction in lung function measurements: (1) peak expiratory flow (PEF) monitoring, (2) spirometry with bronchodilation test or (3) test for bronchial hyperreactivity (table 2). To confirm or rule out the asthma diagnosis, the patients carried out a 2-week PEF monitoring, spirometry with bronchodilation test and methacholine challenge test. The PEF monitoring included PEF measurements with Pinnacle peak flow metre for 2 weeks in the morning and evening before and after inhaled bronchodilator (0.4 mg salbutamol).

Table 2 The criteria based on which asthma is diagnosed in different clinical tests[29]

Clinical test	Criteria for asthma
Two-week PEF monitoring	At least three times ► At least 15% and 60 L/min improvements of PEF after bronchodilator. ► Diurnal variation of PEF at least 20% and 60 L/min.
Spirometry	At least 200 mL and 12% improvement in FEV1 or FVC after bronchodilator
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV1 (PD20FEV1 <600 µg)

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow.

Spirometry was performed according to European Respiratory Society/American Thoracic Society guidelines,[30] and methacholine challenge test using dosimeter with controlled tidal breathing according to Finnish guidelines.[31] To investigate if possible asthma is associated with work, the patients performed PEF monitoring at and off work[32] with Vitalograph PEF/FEV Diary device. Diffusing capacity of the lungs[33] and exhaled nitric oxide (FE_{NO})[34] were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-laryngology (JN) and phoniatrics (SV) examined the patients. For diagnosing laryngeal disorders, videolaryngostroboscopy with either rigid or fibre-optic scope was performed, voice samples were recorded and also inspirograms were recorded before and after methacholine tests. Biopsy of nasal mucosa and a blood sample were taken and preserved for later analyses.

Exposure to MD at work was assessed from the documents of the building and indoor air quality investigations made at the workplace, if available, according to Finnish guidelines.[35] A confirmed MD is graded into different severity categories, if sufficient information is available. Also, MMMFs, VOCs or problems in ventilation conditions at workplace were assessed if these had been measured.

As a non-responder analysis, of the patients who were invited but who did not take part in the study, age, symptoms, the presence of asthma diagnosis and exposure will be evaluated based on patient records.

To explore how common laryngeal disorders are in general, methacholine challenge test, voice recording, clinical examination by the specialist of phoniatrics including videolaryngostroboscopy, FE_{NO} and skin prick tests will be conducted to 50 asymptomatic volunteers adjusted for age and gender. The gathering of the volunteers began in August 2018 and it is our estimation that all the volunteers will be examined by the end of 2019.

Questionnaire/survey

The study patients and the volunteers fill out a questionnaire including questions on

- Previous diseases, medication and upper and lower respiratory symptoms.[36]
- Sinusitis symptoms (Sino-Nasal Outcome Test-22[37]).
- Voice symptoms (Voice Activity and Participation Profile,[38] Voice Handicap Index,[39] Voice Disorder Questionnaire[40]).
- Laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire[41]).
- Reflux symptoms (Reflux Symptom Index[42]).
- Depression and anxiety symptoms (General Health Questionnaire GHQ-12[43]; Generalised Anxiety Disorder 7-item scale[44]).
- Psychosocial work load[45] and stress symptoms.[46]
- Chemical sensitivity (QEESI©).[28]

To find out if the study group would have different background characteristics from the overall population, the same questionnaire was sent to 1500 Finnish-speaking people in the same hospital district

randomly selected by the Finnish Population Information System. The proportions of women and men and different age groups in this comparison material are similar to the study population.

Sample size and power calculation

We estimated that a sample of 100 patients is enough to clinical deduction of the different characteristics of this patient group.

Concerning the population-based comparison material, our aim was to get 400 questionnaire answers (ratio 1:4) to increase the statistical power. Taking recent rather low survey response rates into account, we sent the questionnaire to 1500 people.

To assess if findings suggesting laryngeal disorders are more frequent among those who have respiratory tract or voice symptoms associated to workplace MD, data on frequency of laryngeal findings of asymptomatic people are needed. When analysing the findings of methacholine challenge test of 30 patients, signs of laryngeal disorders were found in 62.5%. We estimated that among <30% of asymptomatic people there are such findings in the methacholine challenge test. In power calculation based on findings in the methacholine challenge test, the number of asymptomatic people tested would be 50 with 80% force and 90% CI.

Data analyses

We will analyse descriptive statistics (mean, median or proportion depending on the variable type and distribution) for variables such as gender distribution and age of the patients and their lines of business. We will also analyse the frequencies of different symptoms the patients complain and how these are related to objective findings in different organ systems or new diagnoses of, for example, asthma or laryngeal dysfunction. We will describe the proportions of patients with significant findings in medical assessment at different specialities (ENT, pulmonary and phoniatrics). We will compare frequencies and intensities of different symptoms and clinical findings between the patients and symptomless controls. We will also compare different background factors of the study patients, such as perceived psychosocial work load, with controls of the population who answered to the same questionnaire as the study patients. Dichotomous variables between two groups (patients vs controls or among patients with or without a certain finding) will be compared using $\chi 2$ test and Fisher's exact test, while continuous variables between two groups will be analysed by t-test or Mann-Whitney test depending on the distributions. Multiple logistic regression will be used to assess independent predictors of certain clinical findings among the patients. Based on the relationship between symptoms and different objective findings, we aim to find 'clinical triggers' (certain sets of symptoms) that should prompt clinicians to refer patients to certain specialities.

Patient and public involvement

Patients or public were not involved in the design of the study. The study patients have received the results of their own tests, explanations for them and necessary treatment.

ETHICS AND DISSEMINATION

The regional ethics committee of Tampere University Hospital has approved the study (R14095). All study subjects gave their written informed consent, which is required also from the volunteers. The study adheres to good clinical research guidelines and the Helsinki Declaration.[47]

The results will be communicated locally as well as internationally as conference papers and journal articles.

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Contributors JU is the head of the study group and PN is the principal researcher. All the writers took part in developing the study protocol: JU and PN planning the exposure assessment; JK, LL and AT the lung function diagnostics measures; JN the diagnostics of upper airways and SV, LK and EK the laryngeal investigations. All authors contributed to and approved the manuscript.

Funding This work was supported by the Tampere Tuberculosis Foundation and the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital (grant number 9T069).

Competing interests The study group report grants from Tampere Tuberculosis Foundation, grants from Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, during the conduct of the study.

Patient consent for publication Not required.

Ethics approval The regional ethics committee of Tampere University Hospital has approved the study (R14095).

Provenance and peer review Not commissioned; externally peer reviewed.

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PUBLICATION II

Clinical Findings among Patients with Respiratory Symptoms Related to Moisture Damage Exposure at the Workplace—The SAMDAW Study

Nynäs P, Vilpas S, Kankare E, Karjalainen J, Lehtimäki L, Numminen J, Tikkakoski A, Kleemola L, Uitti J.

Healthcare 2021, 9, 1112. https://doi.org/10.3390/healthcare9091112

healthcare

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Article

Clinical Findings among Patients with Respiratory Symptoms Related to Moisture Damage Exposure at the Workplace—The SAMDAW Study

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Abstract: Background: Respiratory tract symptoms are associated with workplace moisture damage (MD). The focus of this observational clinical study was patients with workplace MD-associated symptoms, to evaluate the usefulness of different clinical tests in diagnostics in secondary healthcare with a special interest in improving the differential diagnostics between asthma and laryngeal dysfunction. Methods: In patients referred because of workplace MD-associated respiratory tract symptoms, we sought to systematically assess a wide variety of clinical findings. Results: New-onset asthma was diagnosed in 30% of the study patients. Laryngeal dysfunction was found in 28% and organic laryngeal changes in 22% of the patients, and these were common among patients both with and without asthma. Most of the patients (85%) reported a runny or stuffy nose, and 11% of them had chronic rhinosinusitis. Atopy was equally as common as in the general population. Conclusions: As laryngeal changes were rather common, we recommend proper differential diagnostics with lung function testing and investigations of the larynx and its functioning, when necessary, in cases of prolonged workplace MD-associated symptoms. Chronic rhinosinusitis among these patients was not uncommon. Based on this study, allergy testing should not play a major role in the examination of these patients.

Keywords: moisture damage; mold; dampness; asthma; irritable larynx; respiratory symptoms; laryngeal dysfunction; workplace

Citation: Nynäs, P.; Vilpas, S.; Kankare, E.; Karjalainen, J.; Lehtimäki, L.; Numminen, J.; Tikkakoski, A.; Kleemola, L.; Uitti, J. Clinical Findings among Patients with Respiratory Symptoms Related to Moisture Damage Exposure at the Workplace—The SAMDAW Study. *Healthcare* **2021**, *9*, 1112. https://doi.org/10.3390/healthcare9091112

Academic Editor: Andrea Tittarelli

Received: 21 June 2021
Accepted: 24 August 2021
Published: 27 August 2021

1. Introduction

Building moisture damage (MD) exposure-associated health effects have been a particular object of research since the 1990s. Epidemiological studies have previously observed that indoor MD exposure is associated with respiratory health effects such as upper respiratory tract symptoms, the development of asthma and asthma deterioration [1–3]. So far, these studies have mainly focused on children's risk of asthma, other respiratory tract symptoms, and MD exposure at home or in schools [4–8], but some previous research has also established a temporal relationship between workplace MD exposure, asthma [9–12] and rhinitis symptoms [13–15].

The above-mentioned epidemiological associations between MD exposure and respiratory tract symptoms and diseases are an important basis of knowledge, but the information on the diagnoses and symptoms of the exposed patients is mostly based on questionnaires. Studies using only questionnaires rather than clinical examinations and tests do not reliably

diagnose asthma, and are also unable to diagnose several other diseases related to dyspnea, hoarseness and nasal blockage [16,17].

To our knowledge, only a few previous studies have performed clinical assessments of people exposed to MD at work. Cox-Ganser et al., in their study of the workers of an office building with MD, found abnormal lung function and/or respiratory medication use in 67% of the workers with respiratory tract symptoms [18]. White et al. discovered signs of work-related peak flow changes in serial measurements of workers in an office building with MD [19]. However, no clinical studies have considered the whole respiratory tract system of people with symptoms at workplaces with MD. Not only pulmonary diseases, but also laryngeal dysfunction may cause dyspnea, hoarseness and coughing [20]. Several studies have described laryngeal symptoms that develop at work and are associated with exposure to fumes, odors, or other airborne substances [21–23]. Cummings et al. described respiratory tract symptoms, asthma, and rhinosinusitis cases in workers of two office buildings with MD, including two cases of vocal cord dysfunction [24]. Otherwise, no studies on workplace MD exposure being associated with laryngeal dysfunction exist.

The Finnish guideline (2016) for examining a patient with symptoms associated with MD instruct doctors to examine patients according to the symptoms they present by following general diagnostics recommendations. Skin prick tests or allergen-specific IgE measurements are often used with patients with respiratory symptoms because atopy is a known risk factor and a phenotypic feature of many known respiratory diseases. Specific IgE antibody tests for molds are not recommended in primary healthcare, and in secondary healthcare they are usually considered necessary only for patients with severe symptoms that suggest allergy or asthma [25]. The diagnosis of occupational asthma due to MD exposure at workplaces in Finland requires an evaluation of microbial exposure and differential diagnostics in secondary healthcare. Other reasons for referral are a suspicion of asthma with normal PEF monitoring and spirometry in primary healthcare—as additional tests such as methacholine challenge test or exercise test are usually performed in secondary healthcare—or difficult symptoms that affect work ability.

The German–Austrian guideline on medical diagnostics for indoor mold exposure (2016) note that mold exposure may cause mucosal irritation, odor harm and general ill-being. The authors have concluded that indoor molds may cause allergic sensitization, but not as often as other environmental allergens [2]. The existing guidelines are mainly based on studies of the health effects of MD exposure at home, and most of these studies have focused on children. The guidelines may not be ideal for examining adults exposed to MD at the workplace because exposure at work is different to that at home and usually lasts for a shorter time each day. In practice, routine allergy and laboratory tests are often used, but there is no evidence of whether they are effective for workplace MD-exposed patients with respiratory tract symptoms.

In Finland, due to commonly experienced indoor air-associated symptoms and a growing public concern over MDs in buildings and their possible permanent effects on workers' health, the Prime Minister's office has set up the project Healthy Premises 2028. Its objectives are to restore public buildings and increase the effectiveness of the treatment and rehabilitation of subjects with indoor air-associated symptoms. The Finnish Institute for Health and Welfare is responsible for executing the project, which aims to enhance the understanding of the effects of indoor environments on health and well-being and to improve the treatment of people with symptoms and illnesses [26].

Improvements in treatment and rehabilitation call for more knowledge on the individual level of the conditions and findings that lie behind MD-associated symptoms, which is why an observational clinical study gathering information systematically was needed.

The focus of this observational clinical study was patients with respiratory tract symptoms associated with MD in the workplace, in order to evaluate the usefulness of different clinical tests in diagnostics in secondary healthcare with a special interest in improving the differential diagnostics between asthma and laryngeal dysfunction.

2. Materials and Methods

The study was conducted at Tampere University Hospital, which is a secondary-level referral center for a population of 530,000 and a tertiary-level referral center for a population of 1.1 million people. All patients referred to the departments of Occupational Medicine or Phoniatrics or the Allergy Centre because of symptoms associated with suspicion of MD at their workplace were interviewed as possible study participants between October 2015 and June 2017. We targeted a sample of 100 patients to enable clinical evaluation of patient characteristics. The study inclusion criteria were (1) age between 18 and 65 years, (2) upper and/or lower respiratory tract and/or voice symptoms that are associated with the workplace, and (3) strong suspicion or evidence of MD at the workplace. The criteria on which MD in the workplace was suspected were as follows: (1) indoor air was perceived as moldy or stuffy or otherwise unpleasant, (2) there were signs of MDs (visible mold, moisture spots, discoloration of surface materials, disengaging or blistering of flooring materials, crumbling of wall plastering, water leakages through ceilings (buckets on the floors), and/or loose water on surfaces), (3) renovations because of MDs previously made in the building, and/or (4) information of MD findings had been received from the employer or occupational and health safety personnel. The exclusion criteria were (1) severe illness (e.g., cancer) and (2) pregnancy.

The study protocol has previously been published in detail [27]. In short, the participants were evaluated by specialists in occupational medicine, respiratory medicine and allergology, otorhinolaryngology (ORL) and phoniatrics. The clinical tests of the study patients included blood samples, comprehensive lung function tests (two-week PEF monitoring with measurements twice a day before and after beta-agonist, spirometry with bronchodilation test, methacholine challenge test, a pulmonary diffusing capacity and exhaled nitric oxide (FeNO)), and chest X-ray and cone beam computed tomography (CBCT) imaging of the paranasal sinuses.

Asthma was diagnosed based on symptoms and the demonstration of reversible or variable airway obstruction in lung function measurements: (i) peak expiratory flow (PEF) monitoring, (ii) spirometry with bronchodilation test, or (iii) methacholine challenge test [27]. If the respiratory specialists considered it necessary, the selected patients underwent additional tests such as (high-resolution) computed tomography (CT/HRCT) of the thorax, eucapnic voluntary hyperventilation, or (cardio-pulmonary) exercise tests.

In the ORL specialist's clinical evaluation, the diagnostic criteria for chronic rhinosinusitis (CRS) were in accordance with the EPOS2012 guideline [28], with symptoms of nasal discharge, nasal blockage, hyposmia, facial pressure/pain or nocturnal coughing for at least 12 weeks and signs of pus in the middle meatus, or pathologic imaging findings in CBCT scans. The CBCTs were also assessed using Lund–Mackay scoring [29].

An experienced phoniatrician assessed the participants' laryngeal status by indirect video laryngostroboscopy with a 90° rigid telescope (Olympus, Hamburg, Germany), a flexible fiberscope (ENF Type GP, SD video, Olympus, Hamburg, Germany) or a flexible naso-pharyngo videoscope (chip in tip, HD video, Olympus, Hamburg, Germany) with straight and strobe light. Sprayed local anesthesia (Xylocain spray) was used to avoid the gagging reflex. To analyze the video recordings, we used the rpSzene® system (Rehder/Partner GmbH, Hamburg, Germany). We followed international guidelines to diagnose laryngeal dysfunctions and organic laryngeal diseases [30–32].

Skin prick testing (SPT) was conducted for common allergen extracts (birch, timothy, mugwort, horse, dog, cat, house dust mite Dermatophagoides pteronyssinus, and latex) (Soluprick SQ, ALK A/S, Copenhagen, Denmark) and *Aspergillus fumigatus* (Soluprick, ALK A/S, Copenhagen, Denmark). These were carried out by trained nurses according to a standardized protocol [33]. The SPT was considered positive, showing sensitization to the allergen, if the wheal size was at least 3 mm larger than the negative control.

IgE antibodies to different fungi that can be found in building structures with MD (*Aspergillus fumigatus*, *Aspergillus versicolor*, *Acremonium kiliense*, *Cladosporium cladosporioides*, *Fusarium moniliformae*, *Penicillium* species, *Stachybotrys atra*, *Trichoderma viridae*) were

analyzed using the ImmunoCAP system (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden) and fluoroenzyme immunoassay (FEIA). Specific IgE $\geq$ 0.35 kU/L was considered positive.

To control for possible bias related to willingness to participate, based on patient records, the age, sex, line of business, main symptoms, asthma diagnosis, and exposure of the patients who were invited but did not take part in the study were evaluated.

To compare the categorical and continuous variables of the study patients, non-participants and patients with and without asthma, independent sample *t*-tests, Chi-Square, and Mann–Whitney tests were used. Data management and analysis were performed using IBM® SPSS® Statistics Version 25 (2017).

The Ethics Committee of the Pirkanmaa Hospital District approved the study (R14095). All the study participants gave their written informed consent.

3. Results

3.1. Study Patients

To reach a sample size of 100 patients, we interviewed 148 patients between October 2015 and June 2017. The reasons for their referral to secondary healthcare were a suspicion of workplace MD-associated asthma or difficult symptoms associated with workplace MD. In total, 12 patients were excluded as they did not fulfil the inclusion criteria or fulfilled an exclusion criterion, 28 did not want to participate, and 108 gave their consent and participated. Nine patients later withdrew their consent. The final study population consisted of 99 patients (Figure 1), 82 of whom were women and 17 men.

The study patients' age varied between 20 and 63 years (mean 44 years). Most of the patients (72%) were referred to secondary healthcare by their occupational health physicians. Nine per cent of them were current smokers, one of whom was male. The education personnel (29%) included 23 teachers, and the rest were other school and academy workers. The patients from health services (26%) were nurses, practical nurses, and assistants. The other patients worked in social services (12%), the civil service and national defense (11%), industry or trade (11%), and other lines of business (10%). Based on referral information and anamnesis, 99% of the patients reported hoarseness, 85% a runny or stuffy nose, 92% coughing, and 86% dyspnea at the workplace. Neither cough nor dyspnea were reported by five patients.

3.2. Clinical Findings of Respiratory Medicine Specialists

New-onset asthma was diagnosed in 30 patients, and 2 patients had had asthma before employment in the workplace with MD. Of the new asthma diagnoses, fifteen were confirmed by PEF monitoring, nine by findings in both PEF monitoring and spirometry and/or the methacholine challenge test, and six patients were diagnosed as having asthma based on only the spirometry or methacholine test results. The mean FeNO was 21.5 (2.6–63.0) ppb and mean blood eosinophil count (B-Eos) was 206 (20–860) cells/μL in the 30 patients with new-onset asthma, while they were 20.6 (3.3–109.2) ppb and 169 (20–1010) cells/μL, respectively, in the non-asthmatics. Among the new asthma cases, FeNO was >50 ppb in two patients and B-Eos was >300 cells/μL in five patients. Seven new-onset asthma patients had either FeNO or B-Eos. Two patients with a smoking history of at least 15 pack-years had mild airway obstruction, and one of them fulfilled the diagnostic criterion of chronic obstructive pulmonary disease (COPD) (post bronchodilation FEV1/FVC < 0.7).

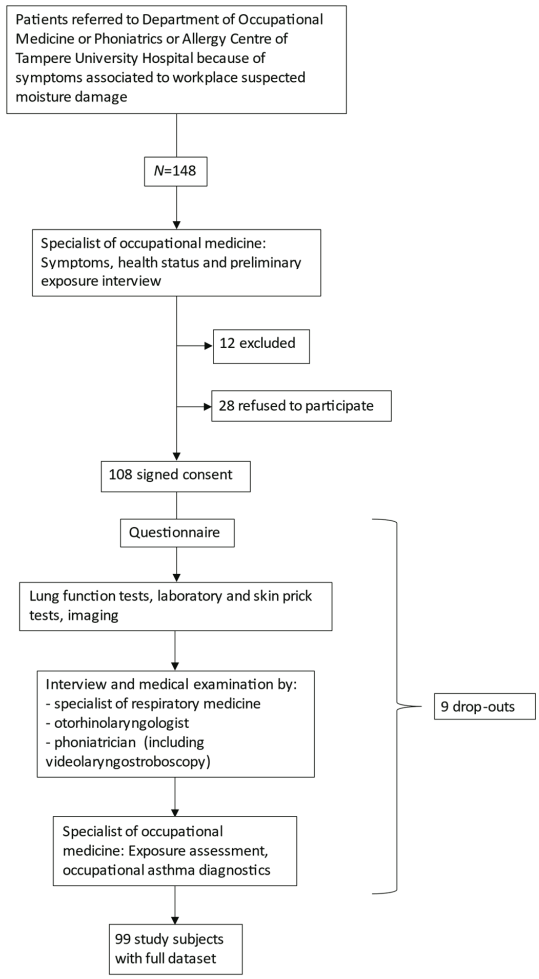

Figure 1. Study design.

The patients' chest X-rays yielded no clinically significant findings. The patients' pulmonary diffusing capacity of carbon monoxide was normal (mean 98% of predicted, range 73–131%). Ten patients were referred for further diagnostic testing by pulmonary specialists (one for HRCT and bronchoscopy, two for polysomnography, four for exercise testing, one for esophageal pH and impedance recording, and three for additional blood tests). Based on these tests, two patients were diagnosed as having hyperventilation syndrome (one of them also had asthma) and one asthma patient was diagnosed with moderate sleep apnea. A CT of the thorax had been programmed for one patient because of a single 6 mm parenchymal nodule detected 20 months earlier. The nodule was unchanged, and no other pathology was found.

3.3. Clinical Findings of Otorhinolaryngology Specialist

Of the 98 patients who underwent the ORL examination, nasal endoscopy revealed that 36 (37%) patients had abnormal findings: 16 (16%) had nasal septal deviation, 9 (9%) had irritated and/or crusty nasal mucosae, 6 (6%) had watery clear discharge, 1 had a nasal septal perforation, and 1 had signs of an acute viral infection. CBCT of the paranasal

sinuses was conducted on all the study patients. The EPOS2012 criteria for CRS, including the symptoms and findings from the CBCT images, were met by 11 (11%) patients. Two additional patients had a Lund–Mackay score of over 4 points, but they had no symptoms compatible with CRS. The CBCTs showed that 34 (34%) patients had anatomical abnormalities such as concha bullosa or hypoplastic paranasal sinuses, 28 (28%) had swollen mucosa in their nasal cavities or in paranasal sinuses, 7 (7%) had high dental roots, 5 (5%) had signs of previous endoscopic sinus surgery, and 8 (8%) had fluid retention in their sinuses. There were no significant differences in FeNO and B-eos or atopic sensitization in patients with or without chronic rhinosinusitis (data not shown).

3.4. Clinical Findings of Phoniatrician

Organic laryngeal findings were observed in 21 (22%) of the 96 participants who underwent the phoniatrician's clinical examination. The organic findings were either mucosal (such as laryngitis, vocal fold polyp, node or other mucosal change, vocal fold atrophy) or neurological (paresis or suspected paresis of recurrent or laryngeal superior nerve). Signs of laryngeal dysfunction were observed in 27 (28%) participants: muscle tensions in the larynx in phonation (primary muscle tension patterns), signs of glottic or supraglottic constriction during breathing at rest, or hyperpnea. Vocal cord dysfunction (VCD) was found in three (3%) patients. There were no significant differences in FeNO and B-eos or atopic sensitization in patients with or without laryngeal problems (data not shown).

Table 1 shows the laryngeal and CRS findings in patients with or without asthma. Altogether, 26 (27%) patients who had undergone examinations by all the specialists ($N = 96$) had neither asthma nor any other pulmonary disease, no clinically relevant results in the ORL examination, and no organic or functional laryngeal findings.

Table 1. Laryngeal and chronic rhinosinusitis findings in patients grouped by asthma diagnosis.

	Asthma ($N = 32$)	No Asthma ($N = 67$)	All ($N = 99$)
Organic or functional laryngeal finding	12 (13% *)	30 (31% *)	42 (44% *)
Chronic rhinosinusitis	4 (13% **)	7 (10% **)	11 (11% **)

* Of the 96 patients who underwent phoniatric examination. ** Of the 98 patients who underwent ORL examination.

3.5. Results of Allergy Tests

Atopy, defined as at least one positive SPT reaction in the standard panel (items 1–8 in Table 2), was found in 37%, and sensitization to any pollen (items 1–3 in Table 2) in 34% of the study patients (Table 2).

Table 2. Positive reactions to specific allergens in skin prick tests of study patients.

Allergen	Positive Reactions (%)
1. Birch	20
2. Timothy	23
3. Mugwort	15
4. Horse	5
5. Dog	16
6. Cat	10
7. *Dermatophagoides pteronyssinus*	2
8. Latex	0
9. *Aspergillus fumigatus*	2

Comparison of the study patients with asthma ($n = 32$) and without asthma ($n = 67$) revealed no significant differences in the rates of sensitization to any of the tested common allergens—46% vs. 33% ($p = 0.275$)—or *Aspergillus fumigatus*—3% vs. 1.5% ($p = 1.000$). The patients' allergen-specific IgE showed no sensitization to the different fungi investigated.

3.6. Non-Participant Analysis

Of the 28 patients who did not take part in the study, 89% were women. Their mean age was 41, which was three years less than that of the study patients, and varied from 22 to 62 years. The majority (86%) of them reported hoarseness and 31% of them received a new asthma diagnosis when they were examined. The patients who did not take part in the study did not differ statistically significantly from the study patients in terms of age, sex, line of business, symptoms at the workplace, or exposure (data not shown).

4. Discussion

In this clinical observational study of patients with respiratory tract symptoms associated with workplace MD, about one third had new-onset asthma. Other pulmonary diseases were uncommon. Functional laryngeal changes were observed in 28% and organic laryngeal changes in 22% of the patients, and they were seen both among asthma patients and non-asthmatics. Most of the patients (85%) had a runny or stuffy nose, but about a tenth had chronic rhinosinusitis, and none had acute bacterial rhinosinusitis. Atopy was equally common among the patients as in the general population, and there were no differences in sensitization to common allergens or MD exposure-associated fungi among the asthma patients compared to among the non-asthmatics.

In our study population, of the individuals with respiratory tract symptoms such as coughing and dyspnea, only about one-third had lower airway dysfunction compatible with asthma. In other words, most of the patients with symptoms that could be interpreted as asthma showed no evidence of variable or reversible airway obstruction. Symptom-based diagnosis of asthma without lung function testing may also cause considerable over-diagnosing of asthma in patients with symptoms related to MD, as many of them probably have laryngeal symptoms only and not true asthma [16,17].

Interestingly, only 7 of the 31 new-onset asthma cases had signs of type 2 inflammation (2 had increased FeNO and 5 had increased levels of blood eosinophils). The proportion of type 2 asthma in our study population was much lower than that usually seen in adult-onset asthma [34,35]. A possible explanation for this is that MD is associated with asthma caused by chronic low-level irritation, which in turn is associated with non-eosinophilic endotypes of asthma [36].

None of the patients showed signs of hypersensitivity pneumonitis (HP; extrinsic allergic alveolitis), which some papers have associated with indoor MD exposure [37,38].

Organic laryngeal changes were more common (22%) here than in a previous study of 78 healthy Finnish female teachers, which found organic laryngeal changes in 14% of the cases [39]. However, no previous research is available on how common functional laryngeal changes are among individuals with or without symptoms. A recent meta-analysis estimated that the prevalence of laryngeal dysfunction among adult asthmatics is 25% [40], which is in line with our study. Respiratory tract symptoms could also be explained by an irritable larynx (IL), a term referring to a hyperreactive larynx leading to increased muscle tension in the laryngeal muscles, dyspnea due to laryngeal constriction, coughing, and voice problems [41]. Our study does not enable us to make conclusions regarding whether MD exposure could cause IL or whether IL is the primary reason for symptoms in a workplace with MD. Either way, in the case of laryngeal disorders, asthma medication does not help or may even worsen symptoms if the larynx is sensitive to irritation [42]. Coexisting with asthma, symptoms of laryngeal origin may be misinterpreted as an insufficient response to asthma treatment. Thorough differential diagnostics and the correct use of asthma medication are thus recommended to avoid unnecessary prolonged symptoms.

Hoarseness was reported by 99% of the patients, but at the first study visit its severity was not evaluated. Hoarseness meant a mild sensation of the voice getting lower for some patients, and complete temporary loss of voice for others. According to previous studies, voice disorders are seen much less in the general population, reported by 17–39% [43,44]. The prevalence of voice disorders among teachers and day care center teachers is high [45,46], but in this study most of the patients were from occupations that

are not especially demanding concerning the use of voice. Hoarseness among the patients without laryngeal findings could be associated with other factors than voice strain, such as actual irritative effect of MD exposure or psychological factors [47].

Most of the patients (85%) reported having a runny or obstructed nose in the workplace, but clinical findings in the ORL examination were rather infrequent. None of the patients had acute bacterial rhinosinusitis. Overall, the clinical findings in the upper respiratory tract seemed to be rather modest in the study population, suggesting that most MD exposure-associated nasal symptoms are attributed to irritation by indoor air impurities. Together with nasal congestion, a sensation of paranasal sinus pressure is often reported by MD-exposed patients [24]. Tools are needed to differentiate congestion symptoms from acute or chronic rhinosinusitis among these patients.

In a study of a random sample of 498 individuals aged 26–60 living in Helsinki, Finland, the results were at the same level as those in our study for SPT positivity to birch (19%), horse (5%), and *Dermatophagoides pteronyssinus* (5%), somewhat lower for SPT positivity to timothy (18%) and mugwort (11%), and were higher to cat (20%) and dog (22%). The frequency of sensitization to any pollen (birch, timothy, mugwort) was 33%, which was as common as among our study patients (34%) [48]. Atopy was equally common among the patients with and without asthma. This finding agrees with a review by Mendell et al. (3) which found MD exposure-associated health effects in both allergic and nonallergic persons.

Based on previous research, CRS, allergic rhinitis and asthma are significantly interrelated in the general population [49]. However, within our study population, no such interrelation was found. This may be due to the fact that atopic sensitization or type 2 inflammation was not common among the patients in the current study, and these seemed not to be associated with asthma, CRS or laryngeal findings in this study.

Aspergillus fumigatus is an easily sporulating fungus found abundantly in the soil [50]. Sensitization to *Aspergillus fumigatus* is linked to severe asthma [51,52], and the fungus is commonly found in the airways of patients with asthma, regardless of the difficulty of their disease [53]. There is evidence that sensitization to *Aspergillus fumigatus* in individuals with asthma becomes more prevalent with increasing age [54]. In a study by Jaakkola et al. of 21–63-year-olds with recently diagnosed asthma in the same province as our study, the prevalence of serum IgE antibodies against *Aspergillus fumigatus* was 5% in the asthma patients and 2% in the population controls [55]. In another Finnish study, in which the mean age of the participants with asthma was 59, 11% of the asthma patients and 4% of the population controls had positive SPT reactions to *Aspergillus fumigatus* [56]. In our study, sensitization to *Aspergillus fumigatus* among patients was low and in line with previous studies in Finland. In population studies in other European and North American countries, the prevalence of sensitization to *Aspergillus fumigatus* was at the same level (3–6%) [57,58].

Overall, since atopy was equally as common among the patients as in the general population, the SPTs for Aspergillus fumigatus were negative, the specific IgE levels of MD-associated fungi were low, and there were no differences in sensitization to common allergens or MD exposure-associated fungi between the asthma patients and the non-asthmatics, routine testing for possible sensitization among these patients is not useful.

In Finland, located in the subarctic region, it is estimated that 20–26% of hospitals and healthcare centers and 12–18% of schools and kindergartens have significant MD, whereas in office buildings the respective proportion is estimated to be 2.5–5% [6,59]. The higher proportion of teaching and health service personnel among the study patients could at least partly explain the more frequent finding of MD at their workplaces.

About 80% of primary-level teachers in Finland are women [60]. In the Finnish trade union of healthcare employees, 92% of members are women [61]. The high proportion of women in our study is thus at least partly due to more women working in public buildings that have MD. However, there is also evidence that women report more symptoms than men in workplaces with indoor air problems [62], which might also contribute to the female predominance in our sample.

Smoking was somewhat less frequent among the study patients than among the Finnish general population: according to the Finnish Institute for Health and Welfare, in 2017, 13% of 20–64-year-old Finns smoked daily [63]. Therefore, smoking does not explain the symptoms that these patients connect to indoor air problems [62]. In Finnish workplaces, smoking has been forbidden by law since 1995, so exposure to passive smoking at the workplace is not a plausible cause of indoor air symptoms.

Our study sample represented a population with respiratory tract symptoms suspected of being related to workplace MD exposure who had been referred to secondary healthcare. We estimated that a sample of 100 patients would be enough for the clinical evaluation of patient characteristics. The study design and sample size do not enable estimation of whether workplace MD exposure is a risk factor for developing a disease; the main aim of this study was to describe the results and diseases found among individuals who are referred to secondary healthcare due to symptoms associated with workplace MD. Of all the workers exposed to MD at the workplace, only those who have symptoms (either due to MD exposure or co-existing with MD exposure) contact their occupational health services and may eventually be referred to secondary care. Thus, the patients in this study were a selected group of workers, whose probability of having asthma was higher than that of the general population or even of workers exposed to MD. No similar previous studies exist for comparison, and this kind of study design prevents any conclusions from being drawn regarding asthma incidence related to workplace MD exposure. However, based on this study, future research is needed to clarify certain points. Laryngeal findings were common in this patient group, but this finding requires confirmation, e.g., by comparison to laryngeal findings of symptomless subjects. The proportion of type 2 asthma in our study population was much lower than that usually seen in adult-onset asthma. The assessment of whether workplace MD-associated asthma is different from asthma in general calls for follow-up research and studies with sputum samples of bronchial biopsies. Means to recognize patients with true rhinosinusitis amongst the patients with upper respiratory tract symptoms are needed.

This kind of comprehensive clinical study, describing findings in patients with symptoms associated with workplace MD exposure, has not been conducted before. Its strength is in its extensive systematic clinical testing and specialist evaluations of the patients exposed to MD in the workplace, increasing the understanding of symptoms and diagnoses and of whether they relate to the symptoms experienced. The non-participants did not differ significantly from the study patients, which reduces the possibility of bias related to willingness to participate in the study.

5. Conclusions

In this study of patients exposed to MD at the workplace and suffering from respiratory tract symptoms, functional or organic changes in the larynx were frequent and common among patients both with and without asthma. Verification of this finding requires further research. Means to recognize patients with true rhinosinusitis and avoid unnecessary treatment with antimicrobial medication due to alleged acute bacterial rhinosinusitis among these patients are needed. However, some suggestions concerning clinical examinations of these patients can be presented already at this point. To avoid unnecessary or symptom-worsening asthma medication, proper differential diagnostics with lung function testing and, when necessary, evaluation of the larynx and its functioning are needed. We conclude that allergy tests do not seem to play a major role in the examination of respiratory symptoms associated with workplace MD exposure.

Author Contributions: Conceptualisation and methodology, J.U., P.N., L.L., J.K., A.T., J.N., S.V., L.K. and E.K.; software, A.T.; formal analysis, P.N.; investigation, P.N., L.L., J.K., S.V., E.K.; data curation, P.N., A.T.; writing—original draft preparation, P.N.; writing—review and editing, P.N., J.U., L.L., J.K., A.T., J.N., S.V., L.K. and E.K.; visualisation, P.N.; supervision, J.U.; project administration, P.N.; funding acquisition, P.N., S.V. and L.K. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Tampere Tuberculosis Foundation, the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (grant number 9T069), the Orion Research Foundation sr., the Research Foundation of the Pulmonary Diseases, the Finnish Medical Foundation, and The Finnish ORL-HNS Foundation.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Pirkanmaa Hospital District (protocol code R14095 and date 7 October 2014).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors thank study nurses Tiina Mäki and Piitu Oksanen for their work in the project and Anna-Maija Haapala, for her help with the laboratory tests.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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PUBLICATION III

Laboratory test results in patients with workplace moisture damage associated symptoms – the SAMDAW study

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Healthcare (Basel)
. 2023 Mar 29;11(7):971. doi: 10.3390/healthcare11070971

healthcare

MDPI

Brief Report

Laboratory Test Results in Patients with Workplace Moisture Damage Associated Symptoms—The SAMDAW Study

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Abstract: The mechanisms of health effects of moisture damage (MD) are unclear, but inflammatory responses have been suspected. The usefulness of laboratory and allergy tests among patients in secondary healthcare with symptoms associated with workplace MD were examined. Full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total serum immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), and skin prick testing were assessed and analyzed in relation to multiple chemical sensitivity (MCS) and perceived stress in 99 patients and 48 controls. In analysis, *t*-tests, Mann-Whitney tests, and chi-squared tests were used. Minor clinically insignificant differences in blood counts were seen in patients and controls, but among patients with asthma an elevated neutrophil count was found in 19% with and only in 2% of patients without asthma ($p = 0.003$). CRP levels and ESR were low, and the study patients' FeNO, total IgE, or allergic sensitization were not increased compared to controls. The level of stress was high among 26% of patients and 6% of controls ($p = 0.005$), and MCS was more common among patients (39% vs. 10%, $p < 0.001$). Stress or MCS were not significantly associated with laboratory test results. In conclusion, no basic laboratory or allergy test results were characteristic of this patient group, and neither inflammatory processes nor allergic sensitization were found to explain the symptoms among these patients. While the value of basic laboratory tests should not be ignored, the use of allergy tests does not seem necessary when symptoms are indicated to be workplace-related.

Keywords: moisture damage; mold; dampness; blood count; CRP; FeNO; IgE; allergy; multiple chemical sensitivity

Citation: Nynäs, P.; Vilpas, S.; Kankare, E.; Karjalainen, J.; Lehtimäki, L.; Numminen, J.; Tikkakoski, A.; Kleemola, L.; Uitti, J. Laboratory Test Results in Patients with Workplace Moisture Damage Associated Symptoms—The SAMDAW Study. *Healthcare* **2023**, *11*, 971. https://doi.org/10.3390/healthcare11070971

Academic Editor: Wolfgang J. C. Uter

Received: 5 February 2023
Revised: 25 March 2023
Accepted: 28 March 2023
Published: 29 March 2023

1. Introduction

Various health effects, such as upper respiratory tract symptoms and the development or deterioration of asthma, have all been associated with exposure to moisture damage (MD) at the workplace [1,2]. The possible mechanisms of health effects associated with MD are unclear but based on findings in some studies, inflammatory responses to MD exposure have been suspected [3]. To prove the development of inflammatory responses studies have explored the levels of C-reactive protein (CRP), blood leucocytes and eosinophils (B-eos), serum total immunoglobulin E (IgE), and fractional exhaled nitric oxide (FeNO) in subjects with MD exposure in different indoor environments. In a study among 6-year-old children with confirmed MD at home, there was a significant positive association between MD exposure and increased serum CRP level. This was not observed with blood leucocyte or FeNO levels [4]. In a ten-year follow-up study among Swedish adults, serum total IgE and CRP levels were found to be predictors of MD-associated symptoms in homes. In the follow-up, smoking decreased, and self-reported hay fever increased significantly while reports of moisture damage at homes somewhat diminished [5].

It must be noted that exposure to possible MD in the workplace differs from that at home: less time is usually spent in the workplace, and the premises, indoor air conditions, especially ventilation, and activities are likewise different. A cross-sectional study using the level of fungal DNA in settled dust as a workplace MD marker revealed elevated levels of CRP and FeNO in employees of Swedish daycare centers with higher fungal DNA levels at the workplace [6]. In another Swedish study with a ten-year follow-up, B-eos was associated with workplace MD at baseline in a random sample of subjects. In the follow-up, MD (self-reported signs of dampness and/or mold odor) was associated with increased symptoms but not with the levels of CRP or serum total IgE [7]. Similar results were obtained in a study with repeated blood samples over 14 months that found no difference in CRP or IgE levels between personnel of MDd and control buildings [8].

Multiple chemical sensitivity (MCS) is a condition in which an individual develops symptoms in different organ systems related to low-level chemical exposure that is not known to cause health effects and does not usually cause symptoms in people [9]. MCS is a subtype of environmental intolerance (EI) [10] which includes reacting to different environmental factors such as chemicals or odors. EI can also be building-related [11]. EI symptoms cannot be explained by any known toxicological [12], physical [13], or immunological [14], mechanisms [15]. Recent studies suggest that the key mechanisms causing EI could be central sensitization and change in the neurological processing of sensory stimuli [11,16,17]. The development of MCS has been linked with perceived stress [18] which on the other hand has been found to associate with both indoor air-associated symptoms [19] and inflammatory responses [20]. As there is no recognized biological mechanism explaining MCS, there are no clinical tests for the diagnosis. To screen the presence of MCS, different questionnaires have been developed of which The Quick Environmental Exposure and Sensitivity Inventory (QEESI©) [21] seems to be the most widely used.

The existing guidelines [22,23] to examine patients with MD-associated symptoms are mainly based on studies of the health effects of MD exposure at home, and most of these studies have focused on children. According to German-Austrian guidelines, doctors are encouraged to assess family medical history regarding allergies even if the significance of predisposition to allergies in MD-associated symptoms is unclear [22]. Routine laboratory and allergy tests are often used when assessing patients with symptoms associated with workplace MD in health care. However, there was and remains a lack of clinical research on patients with workplace MD exposure-associated symptoms. In this study, the aim was to examine the usefulness of laboratory and allergy tests among these patients as a part of their comprehensive clinical evaluation. In addition, associations between MCS and work-related stress and laboratory test findings were investigated.

2. Materials and Methods

Patients who were referred to the Tampere University Hospital departments of Occupational Medicine, Phoniatrics, or the Allergy Centre for evaluation of respiratory or voice symptoms associated with MD exposure at the workplace were recruited to the study. The study inclusion criteria were (1) age between 18 and 65 years, (2) upper and/or lower respiratory tract and/or voice symptoms that are associated with the workplace, and (3) strong suspicion or evidence of MD at the workplace. The exclusion criteria were (1) severe illness (e.g., cancer) and (2) pregnancy. Comprehensive tests and clinical examinations were previously conducted to diagnose possible asthma and chronic rhinosinusitis (CRS). Laboratory tests included single analyses of full blood count, erythrocyte sedimentation rate (ESR), CRP, total serum IgE, and FeNO. Since smoking may cause elevated leucocyte levels [24] and decrease FeNO [25], total leucocyte count (TLC) was analyzed separately in non-smokers and FeNO was omitted from smokers' testing. Skin prick testing (SPT) was conducted using common allergen extracts (birch, timothy, mugwort, horse, dog, cat, house dust mite *Dermatophagoides pteronyssinus*, latex, and *Aspergillus fumigatus*) (Soluprick, ALK A/S, Copenhagen, Denmark). These were carried out by trained nurses according to

a standardized protocol [26]. The SPT was considered positive for allergic sensitization if the wheal size was at least 3 mm larger than the negative control (saline).

In addition, each patient filled out a questionnaire including QEESI© which has been developed for use in research as well as a clinical evaluation of MCS. Three QEESI© subscales were used to assess possible MCS: the chemical intolerance subscale to identify which chemicals or odors are suspected to cause symptoms, the symptom severity subscale to examine the nature and severity of symptoms a person commonly experiences, and the life impact subscale to assess how the sensitivities affect different aspects of everyday life. The respondents rated each item in different subscales between 0 and 10 points, 0 meaning not at all a problem and 10 severe or disabling problems. The points of each subscale were tallied to obtain a total score from 0 to 100. A high score (40–100 points) in the chemical intolerance subscale was used as a criterion for MCS [21].

Work-related stress was assessed with a validated single-item question "Stress means a situation in which a person feels tense, restless, nervous, or anxious or is unable to sleep at night because his/her mind is troubled all the time. Do you feel this kind of stress these days?" by using a 5-point Likert scale from 0 "not at all" to 4 "very much". The responses were dichotomized into a low-stress level (responses from 0 to 2) or a high-stress level (3 and 4) [27].

Symptomless subjects with similar proportions of women and men in different age groups as in the study population were recruited as controls. Except for the absence of the CRP measurement, the controls were subject to the same laboratory tests as the patients.

To compare continuous variables, the independent samples *t*-test and Mann-Whitney test were used. The distributions of the parameters were analyzed from descriptives (differences between mean and 5% trimmed mean, skewness), Q-Q plots, and histograms. For categorical variables, the chi-squared test was used. Data management and analysis were performed using IBM® SPSS® Statistics Version 28 (2021).

The Ethics Committee of the Pirkanmaa Hospital District approved the study (R14095), and all the study participants gave written informed consent.

3. Results

The study population consisted of 99 patients, of whom 82 (83%) were women and 17 (17%) were men. Their age varied between 20 and 63 years (mean 44 years). Of the 48 controls, 37 (77%) were women and 11 (23%) were men, their ages varying between 21 and 60 (mean 44) years.

3.1. Laboratory Test Results

3.1.1. Blood Count

The blood count results were normally distributed both among the patients and the controls except for the eosinophil and basophil counts that were skewed. TLC was 2.7–14.9 $\times 10^9$/L in the patients (mean 6.6 $\times 10^9$/L) and 2.7–9.1 $\times 10^9$/L in the controls (mean 5.6 $\times 10^9$/L) ($p < 0.001$). TLC was elevated (>8.2 $\times 10^9$/L) in 17% of the patients and 4% of the controls ($p = 0.050$). In the non-smokers, the respective proportions were 17% and 2% ($p = 0.019$). Among the patients, elevated TLC was found in 28% with and 12% without asthma ($p = 0.108$), and in 18% with and 17% without CRS ($p = 1.000$).

The mean neutrophil count was 3.77 $\times 10^9$/L in the patients and 3.08 $\times 10^9$/L ($p = 0.001$) in the controls. It was elevated (>6.20 $\times 10^9$/L) in 8.1% of the patients and in none of the controls ($p = 0.055$). Among the patients, an elevated neutrophil count was found in 19% of those with asthma and 2% of those without asthma ($p = 0.003$), 9% of those with CRS, and 7% of those without CRS ($p = 0.714$).

Mean lymphocyte counts were 2.08 $\times 10^9$/L in the patients and 1.85 $\times 10^9$/L in the controls ($p = 0.046$), and elevated (>3.50 $\times 10^9$/L) in 4.1% of the patients and none of the controls ($p = 0.329$).

There were no other significant differences in blood counts (red blood cell indices, thrombocyte count, basophils, and monocytes) between the patients and the controls (supplementary data).

3.1.2. Other Inflammatory Markers

Concerning the results of FeNO, ESR, total IgE, and CRP, the distributions were skewed. FeNO (only non-smokers included in the analysis) was 2.6–109 ppb among the patients (median 17.0 ppb) and 5.7–60.5 ppb among the controls (median 17.1 ppb, $p = 0.507$). ESR was 2–40 mm/h among the patients (median 6 mm/h) and 2–22 mm/h among the controls (median 5 mm/h, $p = 0.043$). Total IgE was 0–715 kU/L among the patients (median 30 kU/L) and 1–671 kU/L among the controls (median 30 kU/L, $p = 0.725$) (Table 1).

CRP among the patients varied from <1.0 to 29 mg/L (median 1.20 mg/L).

Table 1. Laboratory test results of the study patients and the controls (FeNO = fractional exhaled nitric oxide, ESR = erythrocyte sedimentation rate, IgE = serum total immunoglobulin E).

Laboratory Test	Value/Range	Study Patients % (n = 99)	Controls (n = 48)	p
FeNO ppb	<25	69.2	80.4	
	25–50	26.4	15.2	0.355
	>50	4.4	4.3	
ESR mm/h	0–30	98	100	
	>30	2.0	0	1.000
IgE kU/L	0–100	83.8	81.3	
	>100	16.2	18.8	0.695

3.2. Allergy Test Results

Positive SPT reactions occurred equally often in the patients and the controls (Table 2).

Table 2. Positive reactions to specific allergens in skin prick tests of the study patients and the controls.

	Positive Reactions (%) within Group		
Allergen	Study Patients (n = 99)	Controls (n = 48)	p
1. Birch	20	27	0.401
2. Timothy	23	23	1.000
3. Mugwort	15	21	0.483
4. Horse	5	6	0.716
5. Dog	16	17	1.000
6. Cat	10	21	0.121
7. Dermatophagoides pteronyssinus	2	8	0.089
8. Latex	0	0	N.A.
9. Aspergillus fumigatus	2	2	1.000

3.3. Work-Related Stress Level and Laboratory Test Findings

The work-related stress level was significantly more often high in the patients than in the controls (26% vs. 6%, $p = 0.005$). The level of perceived stress was related only to an increased count of blood monocytes in the study patients ($p = 0.016$), not to other blood count results, CRP, FeNO, ESR, or total IgE level (supplementary data).

3.4. MCS and Laboratory and Allergy Test Findings

MCS, defined as high scores in the chemical intolerance subscale, was significantly more common among the patients than among the controls (39% vs. 10%, $p < 0.001$). MCS was not associated with the results of blood count, CRP, FeNO, ESR, or total IgE level (supplementary data).

Among the 26% of patients presenting with the most difficult MCS symptoms, that is scoring high in all QEESI© subscales (40–100 points in the chemical intolerance and symptom severity subscales, and 24–100 points in the life impact subscale) B-eos was the only laboratory test showing significantly more elevated (>0.30 $\times$ 10^9/L) values when compared to corresponding results of the rest of the patients (23.1% vs. 8.2%, p = 0.018) (supplementary data). When the patients with the most difficult MCS symptoms were compared to the rest of the patients, no statistically significant differences in the frequency of asthma (39% vs. 30%, p = 0.436), CRS (4% vs. 14%, p = 0.279), and allergic sensitization (35% vs. 40%, p = 0.645) were observed.

4. Discussion

Among patients referred to secondary health care due to workplace MD associated respiratory and/or voice symptoms, slight elevations in blood leucocyte and neutrophil counts were observed. As previously published, 32% of the patients were diagnosed with asthma and 11% with CRS [28]. A statistically significant relationship between findings of elevated leucocyte or neutrophil counts and diagnosed CRS could not be demonstrated, but among patients with asthma, the elevated neutrophil count was more common than among non-asthmatics. This finding does not necessarily indicate that a large proportion of asthma in these patients has associated with airway neutrophilic inflammation, as it can only be reliably assessed from airway samples [29]. A previous finding among these patients was that 23% of the 30 new-onset asthma cases had signs of type 2 inflammation (increased FeNO and/or levels of blood eosinophils) [28]. These results suggest that MD-associated asthma is less often type 2 asthma as usually seen in adult-onset asthma [30]. Serum total IgE levels did not differ between patients and controls which is in line with previous studies among subjects with workplace MD exposure [7,8].

The levels of CRP and ESR were low, indicating a low probability of inflammatory processes or infections explaining the symptoms [31]. The level of CRP has previously been shown to associate with MD in main living areas at home among children [4]. This discrepancy could be attributed to different immunological responses in children, but CRP remaining low among the patients in this study could suggest that it is the quality of MD exposure at a workplace that fails to induce a systemic inflammatory response. Furthermore, the fact that FeNO and B-eos levels remained normal in this patient group contradictory to previous studies among employees of workplaces with MD [6,7] could indicate exposure differences among the patients. A further study could assess CRP, B-eos, and FeNO levels with respect to the extent and location of MD in relation to symptomatic workers.

The level of perceived stress in the study patients was related to an increased count of monocytes. This result is in line with a previous study by Heidt et al. [32] but probably has little clinical importance. The finding of neutrophilia associated with stress in the study by Heidt et al. was not confirmed in this study. Contradictory to some previous studies [33,34] CRP was not associated with perceived stress in this patient group.

Earlier in comparison with the general population, MCS was found common in this patient group [35]. In this study when comparing with asymptomatic controls, this finding was confirmed. There was no difference in allergic sensitization between the patients and the controls, and sensitization was not associated with MCS. MCS was also not connected to other laboratory test results even if eosinophil count was associated with the most severe MCS symptoms among the patients. However, this could not be explained by asthma, CRS, or allergic sensitization.

A limitation of the study is that the tests were conducted only at one time point which, on the other hand, does reflect the usual diagnostic measures taken in outpatient clinics. Due to the study settings, the results of this study need to be interpreted judiciously.

5. Conclusions

In this study examining workplace MD-exposed patients, there was no basic laboratory or allergy test results characteristic of this patient group. The levels of CRP and ESR were low, and the study patients' FeNO, total IgE, or allergic sensitization were not increased. Considering that MD-associated symptoms are difficult enough to require examinations in secondary health care, inflammatory processes should still be excluded from basic laboratory tests. However, the use of allergy tests does not seem necessary when the symptoms are clearly workplace-related.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/healthcare11070971/s1, Table S1: Blood count results among study patients (N = 99) and controls (N = 48); Table S2: Perceived stress and laboratory tests among the study patients; Table S3: La-boratory test results among patients and controls with MCS.; Table S4: Laboratory test results among the study patients scoring high in all QEESI© subscales vs. others.

Author Contributions: Conceptualization, J.U., P.N., L.L., J.K., A.T., J.N., S.V., L.K. and E.K.; methodology, J.U., P.N., L.L., J.K., A.T., J.N., S.V., L.K. and E.K.; software, A.T.; validation, J.U., P.N., L.L., J.K., A.T., J.N. and L.K.; formal analysis, P.N.; investigation, P.N., L.L., J.K., S.V. and E.K.; resources, J.U., J.K., L.L. and P.N.; data curation, P.N. and A.T.; writing—original draft preparation, P.N.; writing—review and editing, P.N., J.U., L.L., J.K., A.T., J.N., S.V., L.K. and E.K.; visualization, P.N.; supervision, J.U.; project administration, P.N.; funding acquisition, P.N., S.V. and L.K. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Tampere Tuberculosis Foundation, the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (grant number 9T069), the Orion Research Foundation sr., the Research Foundation of the Pulmonary Diseases, the Finnish Medical Foundation, and The Finnish ORL-HNS Foundation.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Pirkanmaa Hospital District (protocol code R14095 and date 7 October 2014).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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PUBLICATION IV

Multiple Chemical Sensitivity in Patients Exposed to Moisture Damage at Work and in General Working-Age Population—The SAMDAW Study

Nynäs, P.; Vilpas, S.; Kankare, E.; Karjalainen, J.; Lehtimäki, L.; Numminen, J.; Tikkakoski, A.; Kleemola, L.; Huhtala, H.; Uitti, J

Int. J. Environ. Res. Public Health 2021, 18, 12296. https://doi.org/10.3390/ ijerph182312296

International Journal of
Environmental Research and Public Health

MDPI

Article

Multiple Chemical Sensitivity in Patients Exposed to Moisture Damage at Work and in General Working-Age Population—The SAMDAW Study

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Citation: Nynäs, P.; Vilpas, S.; Kankare, E.; Karjalainen, J.; Lehtimäki, L.; Numminen, J.; Tikkakoski, A.; Kleemola, L.; Huhtala, H.; Uitti, J. Multiple Chemical Sensitivity in Patients Exposed to Moisture Damage at Work and in General Working-Age Population—The SAMDAW Study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 12296. https://doi.org/10.3390/ijerph182312296

Academic Editor: Marloes Eeftens

Received: 22 September 2021
Accepted: 21 November 2021
Published: 23 November 2021

Abstract: A considerable proportion of patients having respiratory tract or voice symptoms associated with workplace moisture damage (MD) could have multiple chemical sensitivity (MCS). MCS is characterized by symptoms of different organ systems in association with low-level chemical exposure. The objective of this study was to assess the prevalence of MCS among patients referred to secondary health care because of respiratory or voice symptoms associated with workplace MD compared to the general working-age population. Using three subscales of the QEESI© questionnaire, we assessed MCS in the study patients and 1500 controls in the same district randomly selected from the Finnish Population Information System. Study patients had significantly more often high scores in chemical intolerance (39% vs. 23%, $p = 0.001$), symptom severity (60% vs. 27%, $p < 0.001$), and life impact subscales (53% vs. 20%, $p < 0.001$). Asthma, chronic rhinosinusitis, laryngeal problems, and atopy were not associated with the presence of MCS. MCS is common among patients referred to secondary health care with respiratory tract and/or voice symptoms associated with workplace MD, and it considerably affects their everyday life. MCS should be considered as a possible explanatory factor for MD-associated symptoms.

Keywords: multiple chemical sensitivity (MCS); chemical intolerance; moisture damage; mold; dampness

1. Introduction

Multiple chemical sensitivity (MCS) (or chemical/odor intolerance) is a condition characterized by symptoms of different organ systems in association with low-level chemical exposure that is below known harm-causing levels and does not cause symptoms in most people [1]. MCS is a subtype of idiopathic environmental intolerance (IEI) [2], which includes reacting to different environmental factors such as chemicals or odors, electromagnetic fields [3], noise [4], or buildings the person considers "sick" [5]. IEI symptoms cannot be explained by any known toxicological [6], physical [7], or immunological [8,9] mechanisms, but recent studies suggest that central sensitization and change in neurological processing of sensory stimuli could be the key mechanisms causing IEI [10–13].

A consensus in 1999 set six different criteria for a diagnosis of MCS: the condition is chronic, and symptoms are reproducible, appear in multiple organ systems, occur in response to low-level exposure to different chemicals, and resolve after exposure is

ceased [14]. Later, Lacour et al. emphasized the presence of central nervous system symptoms such as headache, fatigue, and cognitive deficits [15]. As there is no recognized biological mechanism explaining MCS, there are no clinical tests for the diagnosis. To screen the presence of MCS, different questionnaires have been developed [16–20] of which the Quick Environmental Exposure and Sensitivity Inventory (QEESI©) [21] seems to be the most widely used [22–28]. However, there are still no commonly accepted definition and diagnostic criteria for MCS [29].

Epidemiological studies on self-reported MCS during the last decade have presented prevalence between 3% and 26%, being often higher in women than in men [22,28,30–34]. Recent research suggests that MCS perhaps is not as permanent a condition as previously thought [35,36]; Palmquist reported 44% of subjects with specific environmental intolerance (EI) recovering during a six-year follow-up. On the other hand, there was a 13% probability that a certain EI would spread to another type of EI [37]. Regardless, MCS may significantly affect the quality of some subjects' social and occupational life [23,38].

Previous epidemiological research has concluded that workplace moisture damage (MD) exposure increases the risk of new-onset asthma and respiratory tract symptoms [39,40]. In a clinical setting, only a part of the patients examined in secondary health care for MD-associated symptoms are diagnosed with an organic disease such as asthma [41,42], and a considerable proportion of them seem to have symptoms of different organ systems referring to possible MCS [30,43]. It has also been suggested that non-specific building-related symptoms that cannot be explained by actual indoor air conditions and MCS share partly common symptoms and could be explained with similar mechanisms [13]. However, the possibility of MCS is not routinely examined in patients presenting with symptoms associated with MD exposure. To improve the management of these patients and to evaluate if routine assessment of possible MCS should be part of their diagnostic workup, we need to know the prevalence of MCS in these patients.

The specific objective of this study was to assess how common MCS is among patients referred to secondary health care because of respiratory tract or voice symptoms associated with MD at the workplace compared to the general working-age population.

2. Materials and Methods

Patients referred to Tampere University Hospital departments of Occupational Medicine or Phoniatrics or Allergy Centre due to respiratory or voice symptoms associated with MD exposure at workplace were recruited to our study. The study protocol has previously been published in detail [44]. Comprehensive clinical tests were conducted to diagnose possible asthma, chronic rhinosinusitis (CRS), laryngeal problem (dysfunction such as muscle tension in phonation or organic problem such as laryngitis or vocal fold polyp), or atopy (defined by at least one skin prick test positive ($\geq$3 mm) result in standard panel including birch, timothy, mugwort, horse, dog, cat, Dermatophagoides Pteronyssinus house dust mite, and latex) in the patients. The clinical findings of the patients have been presented in a previous article [42]. In addition, patients fulfilled a questionnaire including QEESI© which has been developed for use in research as well as clinical evaluation of patients reporting intolerances [21]. Three QEESI© subscales were used to assess possible MCS: the chemical intolerance subscale to find out which chemicals or odors possibly cause symptoms, symptom severity subscale to examine what kind of and how severe symptoms a person commonly experiences, and life impact subscale to assess how the sensitivities affect different aspects of everyday life (Table 1).

The respondents rated each item in different subscales between 0 and 10 points, 0 meaning not at all a problem and 10 severe or disabling problem. The points of each subscale were tallied to obtain a total score from 0 to 100. In the chemical intolerance and symptom severity subscales, the scores 0–19 were classified as low, 20–39 as medium, and 40–100 as high. In the life impact subscale, the respective scores were 0–11, 12–23 and 24–100. A high score class in the chemical intolerance subscale was used as a criterion for

MCS. Based on previous research, this threshold has sensitivity of 83% and specificity of 84% for MCS [21].

Table 1. QEESI© questionnaire subscales used to assess possible MCS and the assessed items within each subscale.

Chemical Intolerance Subscale	Symptom Severity Subscale	Life Impact Subscale
Engine exhaust	Muscle or joint problems	Diet
Tobacco smoke	Eye or respiratory tract problems	Ability to go to work or school
Insecticides	Heart or chest problems	Furnishing home
Gasoline	Stomach or digestive system problems	Choice of clothing
Paint or paint thinner	Problems with ability to think	Ability to travel or drive a car
Cleaning products	Mood problems	Choice of personal care products
Perfumes or fragrances	Balance or coordination problems	Social activities
Fresh asphalt or tar	Headache or feeling of pressure in the head	Choice of hobbies and recreation
Nail polish, nail polish remover or hairspray	Skin problems	Relationship with spouse and family
New furnishings	Urinary tract or genital problems	Ability to clean home and perform other routine chores

To find out if MCS would be more common among the study patients with respiratory tract symptoms associated with MD at workplace than among general working-age population, the same questionnaire was sent to Finnish-speaking controls of the same province with a population of 510,000. Considering the low response rates in surveys nowadays, to obtain a control group of 400 subjects (ratio 4:1), 1500 20–63-year-old persons with proportions of women and men in different age groups equivalent to the study patient population were randomly selected from the Finnish Population Information System. The questionnaire was sent by mail, and a possibility to answer the questionnaire alternatively online was provided.

Independent-samples T-test and chi-squared tests were used to compare categorical and continuous variables between different groups. Data management and analysis were performed using IBM® SPSS® Statistics Version 25 (2017).

The Ethics Committee of the Pirkanmaa Hospital District approved the study (R14095). All the study subjects provided their written informed consent.

3. Results

The study patient population recruited between October 2015 and June 2017 consisted of 99 patients, 82 of whom were women and 17 men. Their mean age was 44 years (range 20–63).

The questionnaire was sent to the controls in autumn 2017, and 568 (38%) of them responded, six of them on the internet. The mean age of the controls was 46 years (range 21–63), and 87% of them were women and 13% men. Age, sex, and the proportions of women and men in different age groups did not statistically differ between study patients and controls (data not shown).

3.1. Study Patients' QEESI© Results

Among the study patients, 39% had high scores in chemical intolerance, 60% in symptom severity, and 53% in life impact subscales. The gender difference did not reach statistical significance among the study patients in chemical intolerance (43% and 24%, respectively, $p = 0.114$) or symptom severity subscales (60% and 59%, respectively, $p = 0.575$), but women had high scores more often in the life impact subscale (57% and 29%, respectively, $p = 0.033$).

Among the study patients, 32% had asthma, 39% asthma and/or CRS, 42% laryngeal dysfunction or organic change, and 37% atopy. No statistically significant differences were found in the comparisons of subscale results between patients with and without these conditions (Table 2).

Table 2. Proportions of study patients with different illnesses or findings reporting high scores in chemical intolerance, symptom severity, and life impact subscales (CRS = chronic rhinosinusitis).

	Asthma (n = 32)			Asthma and/or CRS (n = 39)			Laryngeal Problem[1] (n = 42)			Atopy (n = 37)		
Subscale	yes %	no %	p	yes %	no %	p	yes %	no %	p	yes %	no %	p
Chemical intolerance	44	37	0.661	42	36	0.675	48	33	0.207	30	45	0.143
Symptom severity	63	58	0.827	59	60	1.000	60	59	1.000	60	60	1.000
Life impact	50	54	0.830	46	57	0.410	56	52	0.837	51	53	1.000

[1] Laryngeal dysfunction or organic change.

3.2. Comparison of QEESI© Results between Study Patients and Controls

The study patients had significantly more often high scores in chemical intolerance (39% vs. 23%, $p = 0.001$), symptom severity (60% vs. 27%, $p < 0.001$), and life impact (53% vs. 20%, $p < 0.001$) subscales than controls (Figure 1). The proportion of subjects scoring high in all the three scales was 26% among the patients and 9% among the controls ($p < 0.001$).

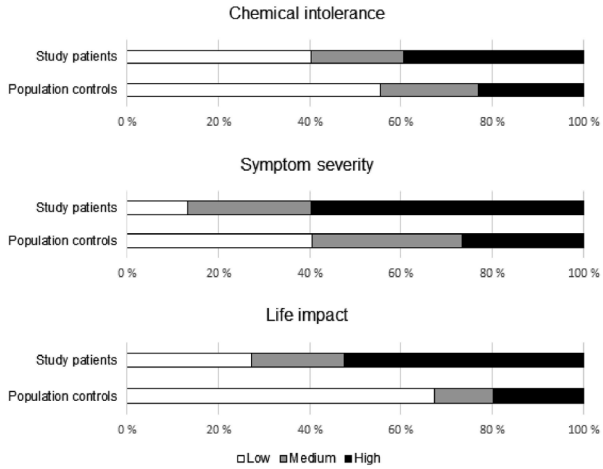

Figure 1. Proportions of subjects with low, medium, and high scores in chemical intolerance ($p = 0.002$), symptom severity ($p < 0.001$), and life impact ($p < 0.001$) among patients and controls (X^2 testing with 3 × 2 crosstabulation).

3.3. Comparison of QEESI© Results between Women and Men among Population Controls

Among the population controls, women had more often high scores in each of the three subscales compared to men: 25% vs. 10% ($p = 0.001$) in chemical intolerance, 29% vs. 10% ($p < 0.001$) in symptom severity, and 22% vs. 5% ($p < 0.001$) in life impact (Figure 2).

3.4. Comparison of QEESI© Results between Population Controls Working and off Work and between Study Patients and Working Controls

Of the population controls, 558 subjects (98%) expressed their employment status: 451 (81%) were currently working and 107 (19%) temporarily (unemployed, students, etc.) or permanently out of work. There were no statistical differences in QEESI© results between those working and off work: they had high scores in the chemical intolerance scale 22% vs. 24% ($p = 0.268$), symptom severity scale 25% vs. 34% ($p = 0.112$), and life impact scale 19% vs. 24% ($p = 0.349$), respectively.

The difference in QEESI© results between working controls and patients (data not shown) was similar to the difference between all the controls and patients presented above.

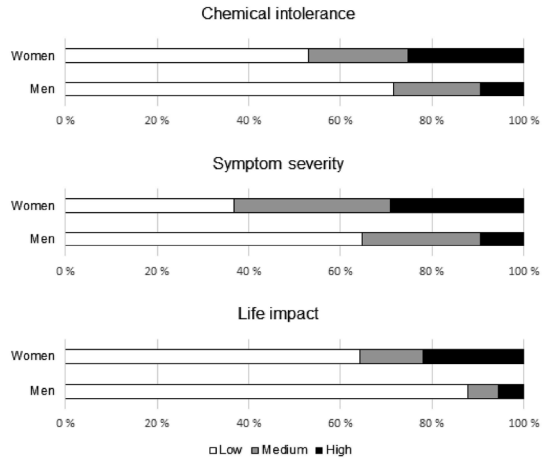

Figure 2. Proportions of controls with low, medium, and high scores in chemical intolerance ($p = 0.004$), symptom severity ($p < 0.001$), and life impact ($p < 0.001$) among women and men (X^2 testing with 3×2 crosstabulation).

4. Discussion

This article presents the first study on workplace-MD-exposed patients' MCS findings compared to the general working-age population. We found that MCS is significantly more prevalent among patients with workplace-MD-associated respiratory tract and/or voice symptoms than among the general population. The most prominent differences between study patients and the general population were in experiencing symptoms and in the effect of sensitivities on different aspects of everyday life.

The prevalence of MCS in the general population was higher in this study (23%) than in the questionnaire study by Karvala et al. (15%) [45]. However, that study was conducted in a certain geographical area in Finland, Ostrobothnia in Western Finland, and the prevalence of self-reported chemical intolerance was assessed with one question. More in line with our study is the study of Vuokko et al. on fertile-age women in Eastern Finland, in which chemical intolerance was determined if the respondent reported intolerance to at least two of the six chemical items asked. Of the respondents, 29% reported annoyance from chemicals without any symptoms and 23% annoyance with one or more symptoms [31]. The prevalence of MCS also varies depending on the target population and on the method and criteria used. Studies with QEESI© on the general population in other countries have resulted in the prevalence of 8–22% depending on the use of different subscale combinations [22,28,46].

Rather than just finding out if a person gets symptoms associated with different chemicals, it would be important to examine how severe the symptoms are and how much the chemical intolerance affects the person's life. In the previously mentioned study of Vuokko et al., 9.9% of the respondents also reported behavioral changes to avoid symptoms and 5.7% disabilities, e.g., disability to work, related to their sensitivities [31]. Respectively, a combination of the three QEESI© subscales (chemical intolerance, symptom severity, and life impact) could be a means of pointing out the most disabling cases of MCS in practice. Receiving high scores in all three subscales indicates that a person gets symptoms in association with several chemicals, has symptoms in different organ systems, and the symptoms considerably affect the person's everyday life. In our study, the proportion of controls receiving high scores in all three subscales was 9%. Of the study patients, 26% received high scores in all three subscales indicating that a considerable proportion of their symptoms could be attributed to MCS.

Whether patients were diagnosed with asthma, asthma and/or chronic rhinosinusitis, laryngeal problem, or atopy or not did not influence MCS findings. This finding is contradictory to previous questionnaire studies reporting MCS being more common among subjects with respiratory tract inflammatory diseases and atopy [43,47,48]. MCS symptoms can, however, be interpreted as respiratory tract disease or allergic symptoms favoring, for example, diagnosis of asthma. It is worth noting that, in the present study, respiratory diseases were not diagnosed based on symptoms only, but asthma was diagnosed based on objective measures of lung function, CRS was diagnosed based on computed tomography and nasal endoscopy, and laryngeal disorders were based on indirect video laryngoscopy.

Women in the general population had more frequently scores referring to MCS compared to men. This finding is in agreement with previous studies [22,45,49], but there is no specific explanation for it. Women reporting more MCS may be linked to, e.g., women having a more sensitive olfactory function [50] or being more worried about possible health effects of environmental factors [51]. Among the study patients, women experienced more difficulties in everyday life because of the sensitivities than men, although there were no significant differences in chemical intolerance and symptom severity subscales. The reason for this is probably that the number of men in study patients was too small to produce statistical significance.

It is thought that MCS could develop after a single exposure event to a chemical (toxicant-induced loss of tolerance) or gradually [52]. Based on this cross-sectional study, it cannot be evaluated if MCS would have originated from MD exposure or if MCS is the primary reason for patients to have symptoms in an MD workplace. Either way, the possibility of MCS explaining at least a part of the patient's symptoms associated with MD exposure at a workplace should be considered. Sufficient differential diagnostics considering the possible organic background of the patient's symptoms is essential. In asthma treatment, the nature of respiratory symptoms requires thorough clarifying to avoid treating MCS symptoms with asthma medication. Since patients with IEI are a heterogenic group, careful multi-professional assessment of an individual patient's situation and the background of the strain they usually have should be considered [53]. Palmquist suggested that psychotherapy aiming at reducing the emotional and behavioral reactions associated with exposure could be advantageous [37]. This seems reasonable as worrying and a negative affect may be connected to the development and permanence of MCS [13,54]. Mindfulness-based cognitive therapy [55], cognitive-behavioral therapy (CBT), or psychoeducation [56], however, have not so far proven to be efficient treatment choices in MCS, which may partly be explained by certain personality traits that some studies have linked with IEI [10]. There is also a possibility of MCS symptoms spontaneously recovering [37], and the knowledge of this could in part promote symptom relief. As regarding any diseases or symptoms, the nature of MCS symptoms should be well explained to the patient.

The strengths of this study are the systematic clinical examinations [44] of workplace-MD-exposed patients with the assessment of possible MCS with a questionnaire charting which chemicals or odors possibly cause symptoms, what kind of and how severe symptoms a person commonly experiences, and how the sensitivities affect different aspects of everyday life, and comparison of MCS results to the general working-age population. As seen in previous studies, MCS prevalence may vary depending on the target population within the same country, which is why the controls were selected to be working-age and from the same region as the patients lived in.

There are some limitations of the study. The response rate in the questionnaire for the controls in this study was quite low (38%), reflecting the willingness to take part in surveys in general nowadays. Even if the gender proportions in all and in different age groups of the study patients and controls were satisfactorily alike, those who are generally interested in the subject and perhaps more concerned about the effects of environmental factors on their health are probably more likely to take part in the survey, possibly causing the prevalence of MCS in the general population to be overestimated. This must be taken into account when interpreting the results, as the difference in the prevalence of MCS in the

study patients and the general population may seem higher than it actually is. The set-up to compare MCS findings in a selected group of patients and the regional population can be questioned as there is limited knowledge on the background factors besides the age and gender of the controls. However, there is no information on, e.g., MCS in different occupations to favor inspection by occupation. Furthermore, considering the present conception of the mechanism of MCS, knowledge on the possible MD exposure of the controls is not essential. In addition, there is no knowledge of MCS/IEI prevalence among different patient groups in secondary health care.

To the best of our knowledge, QEESI© has been validated in the USA [21], Denmark [28], Japan [57], and Sweden [27]. It was chosen to be used in this study because of its properties enabling the evaluation of MCS difficulty and influence on everyday life and therefore seeming reliable to use in the assessment of MCS.

5. Conclusions

In conclusion, MCS is common among patients referred to secondary health care with respiratory tract and/or voice symptoms associated with workplace MD, and the symptoms considerably affect their everyday lives. MCS should thus be considered as a possible explanatory factor for MD-associated symptoms. MCS is common also in the general working-age population, although its prevalence may be overestimated in our study. In the future, follow-up research is needed to clarify the factors that explain the relief or worsening of MCS.

Author Contributions: Conceptualization, P.N., S.V., E.K., J.K., L.L., J.N., A.T., L.K., H.H. and J.U.; Data curation, P.N. and A.T.; Formal analysis, P.N. and H.H.; Funding acquisition, P.N., S.V. and L.K.; Investigation, P.N.; Methodology, P.N., J.K., L.L. and J.U.; Project administration, P.N. and J.U.; Supervision, J.K. and L.L.; Visualization, P.N.; Writing—original draft, P.N.; Writing—review and editing, P.N., S.V., E.K., J.K., L.L., J.N., A.T., L.K., H.H. and J.U. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Tampere Tuberculosis Foundation, Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (grant number 9T069), Orion Research Foundation sr., Research Foundation of Pulmonary Diseases, Finnish Medical Foundation, and Finnish ORL-HNS Foundation.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Pirkanmaa Hospital District (protocol code R14095 and date 7 October 2014).

Informed Consent Statement: Informed consent was obtained from all patients involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Acknowledgments: The authors thank study nurses Tiina Mäki and Piitu Oksanen for their work in the project.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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